CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202207Orig1s000

CHEMISTRY REVIEW(S)

NDA 202207

Kit for the preparation of Lymphoseek® (technetium Tc 99m tilmanocept) Injection
Navidea Biopharmaceuticals, Inc.
425 Metro Place North
Suite 300
Dublin, OH 43017

Summary of the Basis for the Recommended Action
from Chemistry, Manufacturing, and Controls

Indication: [redacted] (b) (4) localization of lymph nodes in pts with melanoma, and with breast cancer

Presentation: The drug product

Consults

Biopharm Recommendation:	NA
Establishments Evaluation Report:	Acceptable
EA –	Categorical exclusion per 21CFR25.31 granted
Statistics –	N/A
Methods Validation –	Not requested
Clinical Pharm –	Acceptable
Microbiology –	Acceptable
Pharm Toxicology –	NA
DMEPA	Proprietary name acceptable

Original Submission: August 10, 2011
Post-Approval CMC Agreements: None

Drug Substance
Tilmanocept [redacted] (b) (4) has a dextran (C-10) backbone conjugated with a linker moiety (an amine terminated "leash") that is subsequently coupled with Diethylenetriamine pentaacetic acid (DTPA) and

mannose moieties. The mannose acts as a substrate for the receptor on MBP and the DTPA serves as a chelating agent for radiolabeling with Technetium Tc99m.

Since Tilmanocept has a dextran backbone, it has a molecular weight distribution (b) (4) carry the amine leash; of those leashes, 3-8 are conjugated to DTPA, 12-20 are conjugated to mannose and 0-17 remain as the free amine. The calculated average molecular weight of tilmanocept will range from 15,281 to 23,45 A re-test of (b) (4) has been established

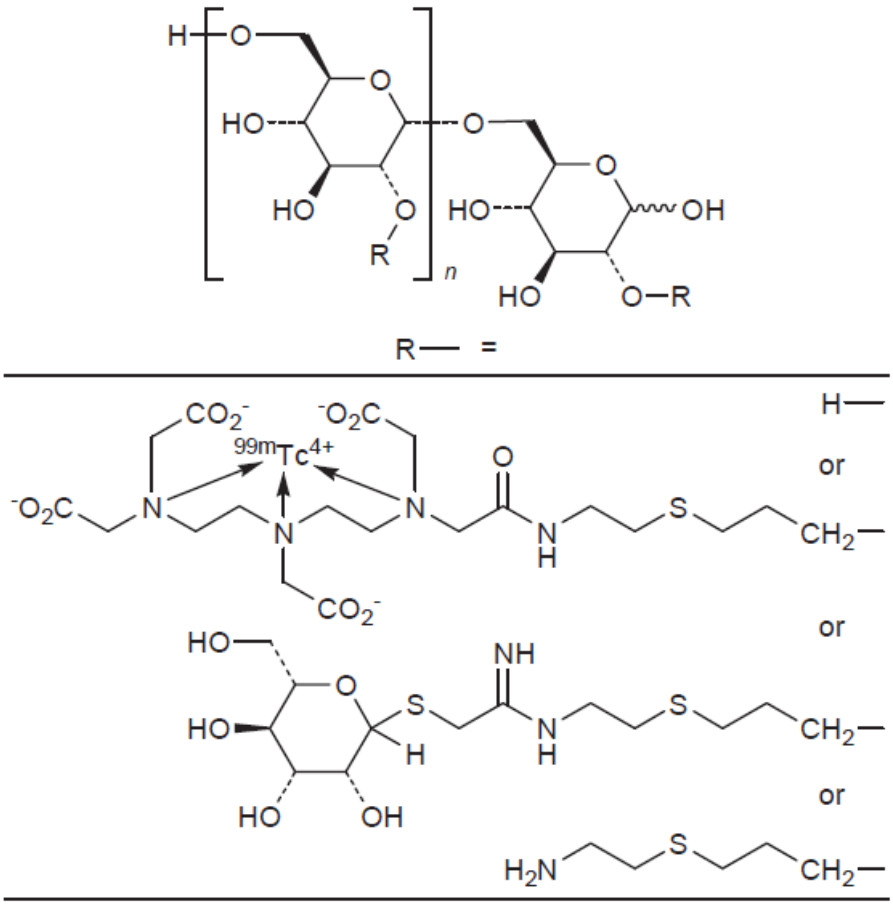
Conclusion: Drug substance is satisfactory

Drug product

The drug product (trademark: Lymphoseek®) will be supplied as "kit" containing a sterile lyophilized preparation of Tilmanocept, 0.25 mg (labeled as Tilmanocept Powder) and co-packaged sterile buffer saline diluent (labeled as DILUENT for Lymphoseek). Tilmanocept Powder vial contains non-radioactive ingredients necessary to produce technetium Tc 99m tilmanocept after radiolabeling with technetium Tc 99m solution obtained from a commercially available generator at the clinical site of use. The Tilmanocept powder vial contains sterile, non-pyrogenic, white to off-white powder, of a mixture of 250 mcg (0.25 mg) of tilmanocept, 20 mg trehalose dihydrate, 0.5 mg glycine, 0.5 mg sodium ascorbate, and 0.075 mg, stannous chloride dihydrate. The contents of the vial are lyophilized and stored under nitrogen. The DILUENT for Lymphoseek contains 4.5 mL sterile buffered saline consisting of 0.04% (w/v) potassium phosphate, 0.11% (w/v) sodium phosphate (heptahydrate), 0.50% (w/v) sodium chloride, and 0.40% (w/v) phenol. The pH is 6.8 – 7.2.

The lyophilized formulation provides (b) (4) lyophilized cake, allowing for quick reconstitution with Sodium Pertechnetate in saline to produce a clear injection solution. Each Tilmanocept powder vial can be radiolabeled with 2.5 – 10 mCi (q.s. 0.35 – 0.7 mL) of sodium pertechnetate solution. The formulation contains (b) (4)

The pH of Lymphoseek powder vial is (b) (4) The diluent is provided to (b) (4) which is considered suitable for parenteral products.



The provided stability data in the NDA support an expiry dating period of 12 months for the drug product.
Drug product is satisfactory

Labeling
Package insert and immediate and carton labeling is acceptable, however, due to the complex nature of product preparation for administration the sponsor developed a "poster" for display in the nuclear pharmacy which succinctly describes the product preparation.

Overall Conclusion:
There are no pending CMC review deficiencies. Therefore, from the CMC point of view, the NDA may be approved.

Eric P. Duffy, Ph.D.
Director, Division III
ONDQA/CDER/FDA

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

/s/

ERIC P DUFFY
02/26/2013

NDA 202207

Kit for the preparation of Lymphoseek® (technetium Tc 99m tilmanocept) Injection

Navidea Biopharmaceuticals, Inc.
425 Metro Place North
Suite 300
Dublin, OH 43017

Ravindra K. Kasliwal, Ph.D.
Division of New Drug Quality Assessment – III
Division of Medical Imaging Products

Table of Contents

Chemistry Review Data Sheet

1. **NDA 202207**

2. REVIEW #: 3

3. REVIEW DATE: 19-Feb-2013

4. REVIEWER: Ravindra K. Kasliwal, Ph.D.

5. PREVIOUS DOCUMENTS:

Submission(s)	Document Date
Original	10-Aug-2011
Amendment	04-Nov-2011
Amendment	06-Jan-2012
Amendment	12-Jan-2012
Amendment	13-Feb-2012
Amendment	17-Feb-2012
Amendment	20-Mar-2012
Amendment	30-Mar-2012
Amendment	05-Apr-2012
Amendment (meeting package)	28-Jun-2012
Amendment	06-Jul-2012
Amendment	02-Aug-2012

6. SUBMISSIONS BEING REVIEWED:

Submission	Document Date
Resubmission	31-Oct-2012
Amendment	09-Nov-2012
Amendment	16-Nov-2012
Amendment	12-Feb-2013
Amendment	13-Feb-2013

7. NAME & ADDRESS OF APPLICANT:

Name: Navidea Biopharmaceuticals, Inc.

Address: 425 Metro Place North, Suite 300, Dublin, OH 43017

Representative: Rodger Brown, Vice President RA/ QA

Telephone: 614-793-7500 x 142

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Lymphoseek®
b) Non-Proprietary Name (USAN): technetium Tc99m tilmanocept
c) Code Name/# (ONDC only): 70-2903
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Radiopharmaceutical

11. DOSAGE FORM: For Injection

12. STRENGTH/POTENCY: 250 micrograms

13. ROUTE OF ADMINISTRATION: Intradermal

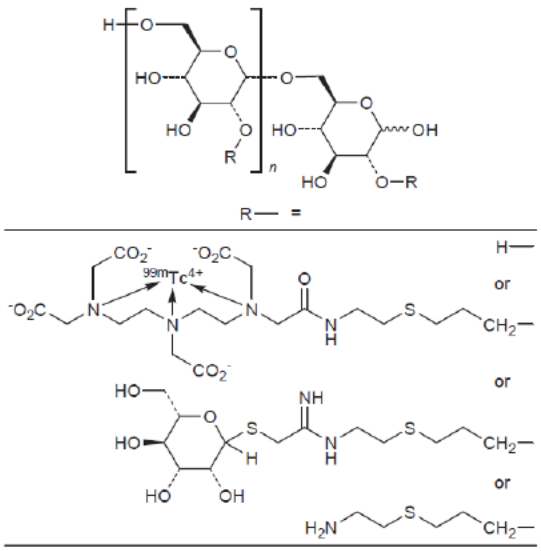
14. Rx/OTC DISPENSED: _X__Rx ___OTC

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

_____SPOTS product – Form Completed

__X___Not a SPOTS product

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



Technetium-^{99}Tc, dextran, 3 [(2-aminoethyl) thio]propyl-17-carboxy-10,13,16-tris (carboxymethyl) -8-oxo-4-thia-7,10,13,16-tetraazaheptadec-1-yl 3-[[2-[[1-imino-2-(D-mannopyranosylthio)ethyl] amino] ethyl] thio]propyl ether.

The molecular formula of technetium Tc 99m tilmanocept is $[C_6H_{10}O_5]_n.(C_{19}H_{28}N_4O_9S^{99m}Tc)_b.(C_{13}H_{24}N_2O_5S_2)_c.(C_5H_{11}NS)_a$
[Where, a = 0-17, b = 12-20, and c = 3-8]

The calculated average molecular weight of tilmanocept will range from 15,281 to 23,454.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	19-Jul-2012	Reviewed by Ravindra K. Kasliwal, Ph.d. and John Metcalf, Ph.D.
	III			4	Adequate	07-Oct-2005	DNF was reviewed for (b) (4) (by Jila Boel, Ph.D.) and was adequate.
	III			4	Adequate	06-Aug-2003	DMF was reviewed for a lyophilized powder product (by Ravindra Kasliwal, Ph.D.) and was adequate.
	V			4	N/A	N/A	The DMF describes (b) (4) and is reviewed by product quality microbiology.
	II			1	Adequate	18-Jul-2012	Reviewed by Ravindra K. Kasliwal, Ph.D.
	III			3, 4	N/A	N/A	The stopper is used in diluent vial. The stopper is used in many injectable products.

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

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

B. Other Documents:

IND 61757	NAVIDEA BIOPHARMACEUTICALS INC 425 METRO PL NORTH STE 450 DUBLIN, OHIO 43017 UNITED STATES	It is referenced in NDA 202207

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not consulted by CMC	N/A	N/A
EES	**Acceptable**	13-Feb-2013	T. Sharp
Pharm/Tox	Approval	26-Jun-2012	Dina A. Olayinka, Ph.D.
Biopharm	Not consulted by CMC	N/A	N/A
LNC	Not consulted by CMC	N/A	N/A
Methods Validation	Will be requested	n/a	n/a
ODS/DMEPA	Properitory name granted.	16-Nov-2011	Jibril Abdus-Samad, PharmD
EA	Claim for categorical exclusion is acceptable	Date of this review.	Ravindra K. Kasliwal, Ph.D.

The Chemistry Review for NDA 202207

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is **recommended for approval action** for chemistry, manufacturing and controls (CMC) under section 505 of the Act.

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

None.

II. Summary of Chemistry Assessments

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

Technetium Tc 99m Tilmanocept binds to receptors on mannose-binding proteins (MBP). Tilmanocept [redacted (b) (4)] has a dextran (C-10) backbone conjugated with a linker moiety (an amine terminated "leash") that is subsequently coupled with Diethylenetriamine pentaacetic acid (DTPA) and mannose moieties. The mannose acts as a substrate for the receptor on MBP and the DTPA serves as a chelating agent for radiolabeling with Technetium Tc99m.

Since Tilmanocept has a dextran backbone, it has a molecular weight distribution [redacted (b) (4)] carry the amine leash; of those leashes, 3-8 are conjugated to DTPA, 12-20 are conjugated to mannose and 0-17 remain as the free amine. The calculated average molecular weight of tilmanocept will range from 15,281 to 23,454. Tilmanocept is an off-white to buff colored powder that is moderately hygroscopic, very water soluble, and insoluble in alcohol. The pH of a 1% solution of Tilmanocept is ≈ 9. Tilmanocept has been observed to degrade only at extreme pH conditions. The degradation is time and temperature dependent [redacted (b) (4)].

The drug product (trademark: Lymphoseek®) will be supplied as "kit" containing a sterile lyophilized preparation of Tilmanocept, 0.25 mg (labeled as Tilmanocept Powder) and co-packaged sterile buffer saline diluent (labeled as DILUENT for Lymphoseek). Tilmanocept Powder vial contains non-radioactive ingredients necessary to produce technetium Tc 99m tilmanocept after radiolabeling with technetium Tc 99m solution obtained from a commercially available generator at the clinical site of use. The Tilmanocept powder vial contains sterile, non-pyrogenic, white to off-white powder, of a mixture of 250 mcg (0.25 mg) of tilmanocept, 20 mg trehalose dihydrate, 0.5 mg glycine, 0.5 mg sodium ascorbate, and 0.075 mg, stannous chloride dihydrate. The contents of the vial are lyophilized and stored under nitrogen. The DILUENT for Lymphoseek contains 4.5 mL sterile buffered saline consisting of 0.04% (w/v) potassium phosphate, 0.11% (w/v) sodium phosphate (heptahydrate), 0.50% (w/v) sodium chloride, and 0.40% (w/v) phenol. The pH is 6.8 – 7.2.

The lyophilized formulation provides [redacted (b) (4)] lyophilized cake, allowing for quick reconstitution with Sodium Pertechnetate in saline to produce a clear injection solution. Each Tilmanocept powder vial can be radiolabeled with 2.5 – 10 mCi (q.s. 0.35 – 0.7 mL) of sodium pertechnetate solution. The formulation contains [redacted (b) (4)]

(b) (4)

The pH of Lymphoseek powder vial is (b) (4). The diluent is provided to (b) (4) which is considered suitable for parenteral products.

The DILUENT for Lymphoseek should be granted a 2 year expiration dating period at controlled room temperature.

For Tilmanocept powder vial a 12 month tentative expiration dating period may be granted when stored at controlled room temperature, 20°C to 25°C (68°F to 77°F). The applicant will have to confirm this from the first three commercial batches that they manufacture and analyze for potency using the new potency method.

The Kit for the preparation of Lymphoseek (technetium Tc99m tilmanocept) injection should be granted a 12 month expiration dating period.

The radiolabeld Lymphoseek (technetium Tc99m tilmanocept) injection should be granted a 6 hour expiration dating period

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

Lymphoseek® (technetium Tc 99m tilmanocept) injection is indicated for intraoperative localization of tumor-draining lymph nodes using a handheld gamma detection probe in patients with breast cancer or melanoma. Prior to administration to the patient, the Nuclear Pharmacy will prepare the injection by taking one lyophilized powder vial and radiolabeling with an amount of radioactivity as Sodium Pertechnetate Tc 99m Injection in isotonic saline. After the prescribed time for the radiolabeling reaction (b) (4) the vial is brought to the prescribed volume using one of the accompanying diluent, Sterile Buffered Saline. It is then QC tested using Instant Thin Layer Chromatography (ITLC) to ensure that the raiochemcial purity is ≥ 90%, and drawn into syringe(s) according to the Physician's order. The Technetium Tc 99m Lymphoseek® Injection is typically administered to patients within a few minutes to a few hours following preparation. Because of the short half-life of the radionuclide and the mode of production, the radiolabeled drug product has a shelf life of six (?) hours.

The patient mass dose in every case is 50 µg. The volume, number of injections and amount of radiation will vary depending on the Physician's orders and the type and time of the scheduled surgery. The maximum reconstitution volume is 5.0 mL. Following lymph node mapping protocol is used.

- Use a handheld gamma counter (represented by any FDA-cleared handheld gamma detection probe) to identify nodes localizing Technetium Tc 99m Lymphoseek Injection. Measure background counts from tissue at least 20 centimeters distal to the injection site. Use the background radioactivity counts plus three standard deviations from the mean background count level (i.e., the three-sigma rule representing >99.7% probable difference from background) as the threshold for positive localization of Technetium Tc 99m Lymphoseek Injection.
- All lymphatic mapping agents use elements of the lymphatic system for distribution. The lymph node localization of Technetium Tc 99m Lymphoseek Injection is dependent upon its binding to reticuloendothelial cells within lymph nodes. Based on clinical studies, the localization and degree of localization (ability to detect multiple nodes with potential anatomic nexuses to the tumor bed) of Technetium Tc 99m Lymphoseek Injection is not dependent on the radiopharmaceutical injection technique. The use of Technetium Tc 99m Lymphoseek Injection is intended to complement palpation, visual inspection, and other procedures important to lymph node localization. Intraoperative lymphatic mapping by gamma detection should be initiated no sooner than (b) (4) post-injection and within (b) (4) of administration of Technetium Tc 99m Lymphoseek Injection.

C. Basis for Not-Approval Recommendation

The application is recommended for approval action because of the following:

1. Determination that sufficient information is provided in this New Drug Application, as amended, to ensure the identity, strength, quality, and purity of the drug substance.
2. Determination that sufficient information is provided in this New Drug Application, as amended, to ensure the identity, strength, quality, and purity of the drug product.
3. The referenced drug master files (DMF) are adequate to support the product application.
4. The microbiology has recommended approval action from product quality microbiology.
5. There are no outstanding issues with specifications, method and impurities.
6. The stability of the Tilmanocept powder vial, the DILUENT for Lymphoseek, as well as the radiolabled product has been sufficiently demonstrated to allow for a reasonable expiration dating period (as indicated above)
7. The CDER office of Compliance, which had previously recommended withhold from approval action, has now recommended (13-Feb-2013) manufacturing and testing facilities are acceptable.
8. The labeling and is found to be acceptable

III. Administrative

A. Reviewer's Signature

Ravindra K Kasliwal, Ph.D.

B. Endorsement Block

Chemist - Name/Date: Ravindra K. Kasliwal/ See DARRTS
Chemistry Division-III Director: Eric P. Duffy, Ph.D. / See DARRTS
Project Manager - Name/Date: Alberta E. Davis-Warren/ See DARRTS

C. CC Block: See DARRTS

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/s/

RAVINDRA K KASLIWAL
02/19/2013

ERIC P DUFFY
02/26/2013

NDA 202207

Kit for the preparation of Lymphoseek® (technetium Tc 99m tilmanocept) Injection

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: Navidea Biopharmaceuticals, Inc.
425 Metro Place North, Suite 300,
Dublin, OH 43017

Indication: Lymphoseek (technetium Tc 99m tilmanocept) Injection is a lymphatic mapping agent indicated for use with a hand-held gamma counter to assist in the localization of lymph nodes draining a primary tumor site in patients with breast cancer or melanoma.

Presentation:
The drug product (trademark: Lymphoseek®) is supplied as "kit" containing a sterile lyophilized preparation of Tilmanocept, 25 mcg (labeled as Tilmanocept Powder) and co-packaged sterile buffer saline diluent (labeled as DILUENT for Lymphoseek). Prior to administration, the Tilmanocept Powder vial is radiolabeled with technetium Tc99m solution at the site of use and then diluted with the supplied diluent.

EER Status: Recommendations: Withold recommendation 30-AUG-2021
(The office of compliance had withhold recommendation as of 25-Apr-2012. This was changed to pending on 09-Aug-2012)

Consults:		
	EA –	Categorical exclusion provided
	CDRH-	N/A
	Statistics –	N/A
	Methods Validation –	Will be requested. Package is provided.
	DEMETS-	Completed
	Biopharm–	N/A
	Microbiology –	Approval
	Pharm/toxicology –	Approval

Original Submission: 10-Aug-2011
Re-submissions: N/A

Post-Approval CMC Commitments:

The applicant commits to provide a statistical analysis of the potency data (for Tilmanocept Powder vial) generated using the new method (SAM3404AR) to determine if the specification can be [redacted] (b) (4) of the labeled amount. The evaluation and justification for the potency specification will be provided in the first annual report.

The applicant commits to test for stability the first three production conformance / validation batches according to the post approval stability protocol. Applicant also commits to test for stability not less than one batch produced during each subsequent year of manufacture according to the post approval stability protocol.

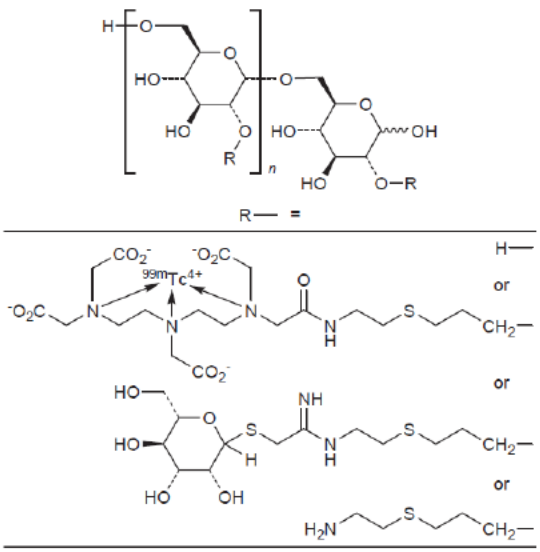
The applicant commits to providing the validation report by 31-Dec-2012 for the HPLC impurities method for tilmanocept bulk drug substance.

Background:
Drug Substance:

Tilmanocept (DTPA Mannosyl Dextran) is manufactured and tested by [redacted] (b) (4). Contract laboratories are used for controlled environmental storage for stability studies, Total Aerobic Microbial Count, Yeasts and Molds testing, heavy metals testing and sodium testing. Tilmanocept drug substance is manufactured [redacted] (b) (4) Details of the conjugation processes and controls are provided and have been reviewed.

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT

Chemical Names



Technetium-^{99}Tc, dextran, 3 [(2-aminoethyl) thio]propyl-17-carboxy-10,13,16-tris (carboxymethyl) -8-oxo-4-thia-7,10,13,16-tetraazaheptadec-1-yl 3-[[2-[[1-imino-2-(D-mannopyranosylthio) ethyl] amino] ethyl] thio]propyl ether.

The molecular formula of technetium Tc 99m tilmanocept is $[C_6H_{10}O_5]_n.(C_{19}H_{28}N_4O_9S^{99m}Tc)_b.(C_{13}H_{24}N_2O_5S_2)_c.(C_5H_{11}NS)_a$; [Where, a = 0-17, b = 12-20, and c = 3-8]

The calculated average molecular weight of tilmanocept will range from 15,281 to 23,454.

In the synthesis of tilmanocept, [redacted]. The information regarding the intermediate is provided in DMF [redacted] The DMF was reviewed and found acceptable. Structural characterization of the drug substance was performed by elelemental analyses, FTIR spectroscopy, ^{1}H and ^{13}C NMR spectroscopy, and laser light scattering for molecular weight. Side by side ^{1}H and ^{13}C NMR spectrum of lot M90612 with and without Technetium ^{99m}Tc radiolabeling was performed for elucidation of structure of the radiolabeled drug substance [redacted]

Tilmanocept has a dextran backbone; it has a molecular weight distribution [redacted] carry the amine leash; of those leashes, 3-8 are conjugated to DTPA, 12-20 are conjugated to mannose and 0-17 remain as the free amine. The calculated average molecular weight of tilmanocept will range from 15,281 to 23,454. Tilmanocept is off-white to buff colored powder that is moderately hygroscopic, very water soluble, and insoluble in alcohol. The pH of a 1% solution of Tilmanocept is ≈ 9. Tilmanocept has been observed to degrade only at extreme pH conditions. The degradation is time and temperature dependent [redacted]

A tilmanocept reference standard was developed as the primary reference standard. The drug substance specifications for impurities were deemed acceptable in consultation with the toxicology reviewer. Tilmanocept specifications include appearance including color, identification, assay, [redacted] heavy metals, water content, residual solvents, bacterial endotoxins, total aerobic microbial counts, yeasts and molds, amine number, DTPA number, Mannose number, and molecular weight. Based upon the completed 24 month stability studies, the retest date is [redacted] from the time of release. The label includes a retest date and recommended storage conditions of [redacted]

Conclusion: The drug substance is satisfactory

Drug Product:

The drug product (trademark: Lymphoseek®) is supplied as "kit" containing a sterile lyophilized preparation of Tilmanocept, 0.25 mg (labeled as Tilmanocept Powder) and co-packaged sterile buffer saline diluent (labeled as DILUENT for Lymphoseek). Tilmanocept Powder vial contains non-radioactive ingredients necessary to produce technetium Tc 99m tilmanocept after radiolabeling with technetium Tc 99m solution

obtained from a commercially available generator at the clinical site of use. The Tilmanocept powder vial contains sterile, non-pyrogenic, white to off-white powder, of a mixture of 250 mcg (0.25 mg) of tilmanocept, 20 mg trehalose dihydrate, 0.5 mg glycine, 0.5 mg sodium ascorbate, and 0.075 mg, stannous chloride dihydrate. The contents of the vial are lyophilized and stored under nitrogen. The DILUENT for Lymphoseek contains 4.5 mL sterile buffered saline consisting of 0.04% (w/v) potassium phosphate, 0.11% (w/v) sodium phosphate (heptahydrate), 0.50% (w/v) sodium chloride, and 0.40% (w/v) phenol. The pH is 6.8 – 7.2.

The lyophilized formulation provides (b) (4) lyophilized cake, allowing for quick reconstitution with Sodium Pertechnetate in saline to produce a clear injection solution. Each Tilmanocept powder vial can be radiolabeled with 2.5 – 10 mCi (q.s. 0.35 – 0.7 mL) of sodium pertechnetate solution. The formulation contains (b) (4)

The pH of Lymphoseek powder vial is (b) (4) . The diluent is provided to (b) (4) which is considered suitable for parenteral products.

The DILUENT for Lymphoseek has a 2 year expiration dating period at controlled room temperature.

For Tilmanocept powder vial a 12 month tentative expiration dating period may be granted when stored at controlled room temperature, 20°C to 25°C (68°F to 77°F). The applicant will have to confirm this from the first three commercial batches that they manufacture and analyze for potency using the new potency method.

The Kit for the preparation of Lymphoseek (technetium Tc99m tilmanocept) injection should be granted a 12 month expiration dating period.

The radiolabeld Lymphoseek (technetium Tc99m tilmanocept) injection should be granted a 6 hour expiration dating period

Conclusion: The drug product is satisfactory.

Overall Conclusion:

The CMC recommendation is approval as all CMC, including microbiology issues have been satisfactorily addresses. The application, however, may not be approved until an overall cGMP recommendation of acceptable is available.

Eric P. Duffy, Ph.D.
Division Director


(b) (4)

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/s/

ERIC P DUFFY
09/05/2012

NDA 202207

Kit for the preparation of Lymphoseek® (technetium Tc 99m tilmanocept) Injection

Navidea Biopharmaceuticals, Inc.
425 Metro Place North
Suite 300
Dublin, OH 43017

Ravindra K. Kasliwal, Ph.D.
Division of New Drug Quality Assessment – III
Division of Medical Imaging Products

Table of Contents

Chemistry Review Data Sheet

1. **NDA 202207**

2. REVIEW #: 2

3. REVIEW DATE: 27-Aug-2012

4. REVIEWER: Ravindra K. Kasliwal, Ph.D.

5. PREVIOUS DOCUMENTS:

Submission(s)	Document Date
Original	10-Aug-2011
Amendment	04-Nov-2011
Amendment	06-Jan-2012
Amendment	12-Jan-2012
Amendment	13-Feb-2012
Amendment	17-Feb-2012
Amendment	20-Mar-2012
Amendment	30-Mar-2012
Amendment	05-Apr-2012
Amendment (meeting package)	28-Jun-2012
Amendment	06-Jul-2012

6. SUBMISSION(S) BEING REVIEWED:

Submission	Document Date
Amendment	02-Aug-2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Navidea Biopharmaceuticals, Inc.
Address:	425 Metro Place North, Suite 300, Dublin, OH 43017
Representative:	Rodger Brown, Vice President RA/ QA
Telephone:	614-793-7500 x 142

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Lymphoseek®
b) Non-Proprietary Name (USAN): technetium Tc99m tilmanocept
c) Code Name/# (ONDC only): 70-2903

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Radiopharmaceutical

11. DOSAGE FORM: For Injection

12. STRENGTH/POTENCY: 250 micrograms

13. ROUTE OF ADMINISTRATION: Intradermal

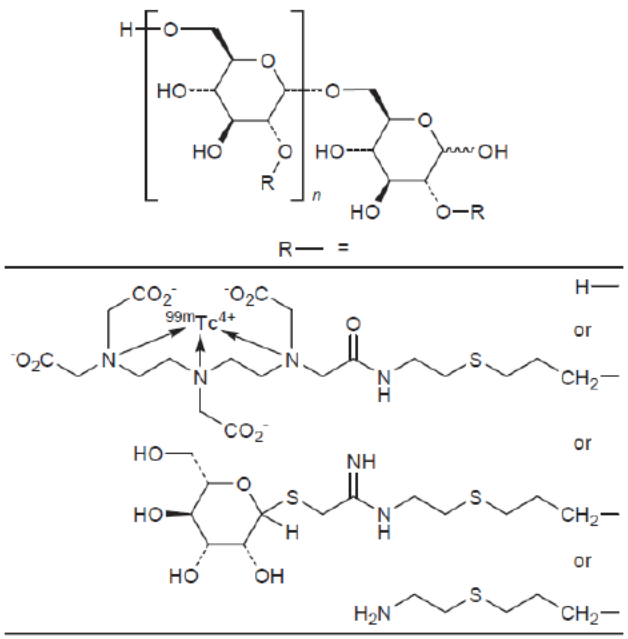
14. Rx/OTC DISPENSED: _X__Rx ___OTC

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

_____SPOTS product – Form Completed

__X___Not a SPOTS product

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



Technetium-^{99}Tc, dextran, 3 [(2-aminoethyl) thio]propyl-17-carboxy-10,13,16-tris (carboxymethyl) -8-oxo-4-thia-7,10,13,16-tetraazaheptadec-1-yl 3-[[2-[[1-imino-2-(D-mannopyranosylthio)ethyl] amino] ethyl] thio]propyl ether.

The molecular formula of technetium Tc 99m tilmanocept is $[C_6H_{10}O_5]_n.(C_{19}H_{28}N_4O_9S^{99m}Tc)_b.(C_{13}H_{24}N_2O_5S_2)_c.(C_5H_{11}NS)_a$
[Where, a = 0-17, b = 12-20, and c = 3-8]

The calculated average molecular weight of tilmanocept will range from 15,281 to 23,454.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	19-Jul-2012	Reviewed by Ravindra K. Kasliwal, Ph.d. and John Metcalf, Ph.D.
	III			4	Adequate	07-Oct-2005	DNF was reviewed for (b) (4) (by Jila Boel, Ph.D.) and was adequate.
	III			4	Adequate	06-Aug-2003	DMF was reviewed for a lyophilized powder product (by Ravindra Kasliwal, Ph.D.) and was adequate.
	V			4	N/A	N/A	The DMF describes (b) (4) and is reviewed by product quality microbiology.
	II			1	Adequate	18-Jul-2012	Reviewed by Ravindra K. Kasliwal, Ph.D.
	III			3, 4	N/A	N/A	The stopper is used in diluent vial. The stopper is used in many injectable products.

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

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

B. Other Documents:

IND 61757	NAVIDEA BIOPHARMACEUTICALS INC 425 METRO PL NORTH STE 450 DUBLIN, OHIO 43017	It is referenced in NDA 202207

	UNITED STATES	

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not consulted by CMC	N/A	N/A
EES	**Pending**	09-Aug-2012 (still same as of the date of this review)	Office of compliance had withhold recommendation as of 25-Apr-2012. This was changed to pending, in view if the changes to the testing methods and facility made by the applicant.
Pharm/Tox	Approval	26-Jun-2012	Dina A. Olayinka, Ph.D.
Biopharm	Not consulted by CMC	N/A	N/A
LNC	Not consulted by CMC	N/A	N/A
Methods Validation	Will be requested	n/a	The package will need to be updated with product specifications and analytical methods and validation data.
ODS/DMEPA	Properitory name granted.	16-Nov-2011	Jibril Abdus-Samad, PharmD
EA	Claim for categorical exclusion is acceptable	Date of this review.	Ravindra K. Kasliwal, Ph.D.

Chemistry Assessment Section

The Chemistry Review for NDA 202207

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is **recommended for approval** for chemistry, manufacturing and controls (CMC) under section 505 of the Act, provided the manufacturing and testing facilities are found to be acceptable by the office of compliance and labeling is found to be acceptable. The office of compliance had withhold recommendation as of 25-Apr-2012. This was changed to pending (09-Aug-2012), in view if the changes to the testing methods and facility made by the applicant.

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

None.

II. Summary of Chemistry Assessments

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

Technetium Tc 99m Tilmanocept binds to receptors on mannose-binding proteins (MBP). Tilmanocept [redacted (b) (4)] has a dextran (C-10) backbone conjugated with a linker moiety (an amine terminated "leash") that is subsequently coupled with Diethylenetriamine pentaacetic acid (DTPA) and mannose moieties. The mannose acts as a substrate for the receptor on MBP and the DTPA serves as a chelating agent for radiolabeling with Technetium Tc99m.

Since Tilmanocept has a dextran backbone, it has a molecular weight distribution [redacted (b) (4)] carry the amine leash; of those leashes, 3-8 are conjugated to DTPA, 12-20 are conjugated to mannose and 0-17 remain as the free amine. The calculated average molecular weight of tilmanocept will range from 15,281 to 23,454. Tilmanocept is an off-white to buff colored powder that is moderately hygroscopic, very water soluble, and insoluble in alcohol. The pH of a 1% solution of Tilmanocept is ≈ 9. Tilmanocept has been observed to degrade only at extreme pH conditions. The degradation is time and temperature dependent. [redacted (b) (4)]

The drug product (trademark: Lymphoseek®) will be supplied as "kit" containing a sterile lyophilized preparation of Tilmanocept, 0.25 mg (labeled as Tilmanocept Powder) and co-packaged sterile buffer saline diluent (labeled as DILUENT for Lymphoseek). Tilmanocept Powder vial contains non-radioactive ingredients necessary to produce technetium Tc 99m tilmanocept after radiolabeling with technetium Tc 99m solution obtained from a commercially available generator at the clinical site of use. The Tilmanocept powder vial contains sterile, non-pyrogenic, white to off-white powder, of a mixture of 250 mcg (0.25 mg) of tilmanocept, 20 mg trehalose dihydrate, 0.5 mg glycine, 0.5 mg sodium ascorbate, and 0.075 mg, stannous chloride dihydrate. The contents of the vial are lyophilized and stored under nitrogen. The DILUENT for Lymphoseek contains 4.5 mL sterile buffered saline consisting of 0.04% (w/v) potassium phosphate, 0.11% (w/v) sodium phosphate (heptahydrate), 0.50% (w/v) sodium chloride, and 0.40% (w/v) phenol. The pH is 6.8 – 7.2.

The lyophilized formulation provides [redacted] (b) (4) lyophilized cake, allowing for quick reconstitution with Sodium Pertechnetate in saline to produce a clear injection solution. Each Tilmanocept powder vial can be radiolabeled with 2.5 – 10 mCi (q.s. 0.35 – 0.7 mL) of sodium pertechnetate solution. The formulation contains [redacted] (b) (4)

The pH of Lymphoseek powder vial is [redacted] (b) (4). The diluent is provided to [redacted] (b) (4) which is considered suitable for parenteral products.

The DILUENT for Lymphoseek should be granted a 2 year expiration dating period at controlled room temperature.

For Tilmanocept powder vial a 12 month tentative expiration dating period may be granted when stored at controlled room temperature, 20°C to 25°C (68°F to 77°F). The applicant will have to confirm this from the first three commercial batches that they manufacture and analyze for potency using the new potency method.

The Kit for the preparation of Lymphoseek (technetium Tc99m tilmanocept) injection should be granted a 12 month expiration dating period.

The radiolabeld Lymphoseek (technetium Tc99m tilmanocept) injection should be granted a 6 hour expiration dating period

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

Lymphoseek® (technetium Tc 99m tilmanocept) injection is indicated for intraoperative localization of tumor-draining lymph nodes using a handheld gamma detection probe in patients with breast cancer or melanoma. Prior to administration to the patient, the Nuclear Pharmacy will prepare the injection by taking one lyophilized powder vial and radiolabeling with an amount of radioactivity as Sodium Pertechnetate Tc 99m Injection in isotonic saline. After the prescribed time for the radiolabeling reaction [redacted] (b) (4) the vial is brought to the prescribed volume using one of the accompanying diluent, Sterile Buffered Saline. It is then QC tested using Instant Thin Layer Chromatography (ITLC) to ensure that the raiochemcial purity is $\geq$ 90%, and drawn into syringe(s) according to the Physician's order. The Technetium Tc 99m Lymphoseek® Injection is typically administered to patients within a few minutes to a few hours following preparation. Because of the short half-life of the radionuclide and the mode of production, the radiolabeled drug product has a shelf life of six (?) hours.

The patient mass dose in every case is 50 µg. The volume, number of injections and amount of radiation will vary depending on the Physician's orders and the type and time of the scheduled surgery. The maximum reconstitution volume is 5.0 mL. Following lymph node mapping protocol is used.

- Use a handheld gamma counter (represented by any FDA-cleared handheld gamma detection probe) to identify nodes localizing Technetium Tc 99m Lymphoseek Injection. Measure background counts from tissue at least 20 centimeters distal to the injection site. Use the background radioactivity counts plus three standard deviations from the mean background count level (i.e., the three-sigma rule representing >99.7% probable difference from background) as the threshold for positive localization of Technetium Tc 99m Lymphoseek Injection.
- All lymphatic mapping agents use elements of the lymphatic system for distribution. The lymph node localization of Technetium Tc 99m Lymphoseek Injection is dependent upon its binding to reticuloendothelial cells within lymph nodes. Based on clinical studies, the localization and degree of localization (ability to detect multiple nodes with potential anatomic nexuses to the tumor bed) of Technetium Tc 99m Lymphoseek

Injection is not dependent on the radiopharmaceutical injection technique. The use of Technetium Tc 99m Lymphoseek Injection is intended to complement palpation, visual inspection, and other procedures important to lymph node localization. Intraoperative lymphatic mapping by gamma detection should be initiated no sooner than (b) (4) post-injection and within (b) (4) of administration of Technetium Tc 99m Lymphoseek Injection.

C. Basis for Not-Approval Recommendation

The application is recommended for approval, provided the manufacturing and testing facilities are found to be acceptable by the office of compliance and labeling is found to be acceptable, because of the following:

1. Determination that sufficient information is provided in this New Drug Application, as amended, to ensure the identity, strength, quality, and purity of the drug substance.
2. Determination that sufficient information is provided in this New Drug Application, as amended, to ensure the identity, strength, quality, and purity of the drug product.
3. The referenced drug master files (DMF) are adequate to support the product application.
4. The microbiology has recommended approval action from product quality microbiology.
5. There are no outstanding issues with specifications, method and impurities.
6. The stability of the Tilmanocept powder vial, the DILUENT for Lymphoseek, as well as the radiolabled product has been sufficiently demonstrated to allow for a reasonable expiration dating period (as indicated above)

III. Administrative

A. Reviewer's Signature

Ravindra K Kasliwal, Ph.D.

B. Endorsement Block

Chemist - Name/Date: Ravindra K. Kasliwal/ See DARRTS
Chemistry Branch Chief - Name/Date: Ali Al-Hakim, Ph.D./ See DARRTS
Project Manager - Name/Date: Alberta E. Davis-Warren/ See DARRTS

C. CC Block: See DARRTS

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/s/

RAVINDRA K KASLIWAL
08/26/2012

ERIC P DUFFY
08/27/2012

NDA 202207

Lymphoseek®
Kit for the preparation of technetium Tc 99m tilmanocept injection

Navidea Biopharmaceuticals, Inc.
425 Metro Place North
Suite 300
Dublin, OH 43017

Ravindra K. Kasliwal, Ph.D.
Division of New Drug Quality Assessment – III
Division of Medical Imaging Products

Table of Contents

Chemistry Review Data Sheet

1. **NDA 202207**

2. REVIEW #: 1

3. REVIEW DATE: 19-Jul-2012

4. REVIEWER: Ravindra K. Kasliwal, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	10-Aug-2011
Amendment	04-Nov-2011
Amendment	06-Jan-2012
Amendment	12-Jan-2012
Amendment	13-Feb-2012
Amendment	17-Feb-2012
Amendment	20-Mar-2012
Amendment	30-Mar-2012
Amendment	05-Apr-2012
Amendment (meeting package)	28-Jun-2012
Amendment	06-Jul-2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Navidea Biopharmaceuticals, Inc.
Address:	425 Metro Place North, Suite 300, Dublin, OH 43017
Representative:	Rodger Brown, Vice President RA/ QA
Telephone:	614-793-7500 x 142

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Lymphoseek®
b) Non-Proprietary Name (USAN): technetium Tc99m tilmanocept
c) Code Name/# (ONDC only): 70-2903
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Radiopharmaceutical

11. DOSAGE FORM: For Injection

12. STRENGTH/POTENCY: 250 micrograms

13. ROUTE OF ADMINISTRATION: Intradermal

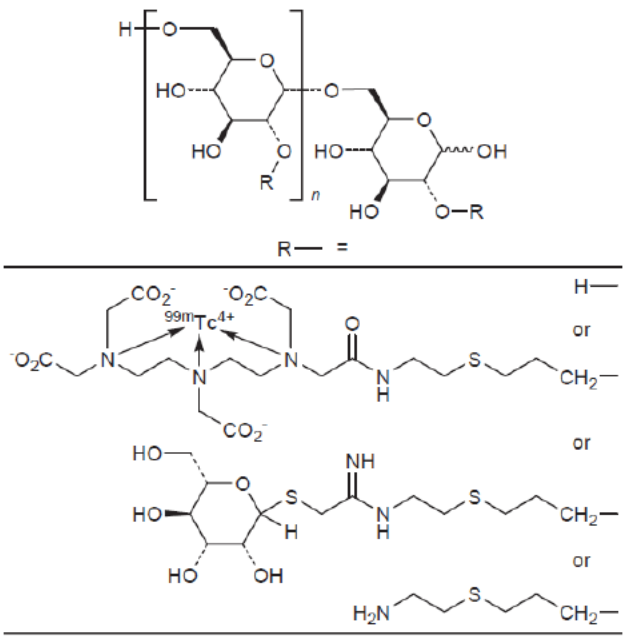
14. Rx/OTC DISPENSED: _X__Rx ___OTC

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

_____SPOTS product – Form Completed

__X___Not a SPOTS product

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



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[Where, a = 0-17, b = 12-20, and c = 3-8]

The calculated average molecular weight of tilmanocept will range from 15,281 to 23,454.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Chemistry Assessment Section

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	19-Jul-2012	Reviewed by Ravindra K. Kasliwal, Ph.d. and John Metcalf, Ph.D.
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6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

IND 61757	NAVIDEA BIOPHARMACEUTICALS INC 425 METRO PL NORTH STE 450 DUBLIN, OHIO 43017 UNITED STATES	It is referenced in NDA 202207

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not consulted by CMC	N/A	N/A
EES	Withhold	25-Apr-2012	Office of compliance.
Pharm/Tox	Approval	26-Jun-2012	Dina A. Olayinka, Ph.D.
Biopharm	Not consulted by CMC	N/A	N/A
LNC	Not consulted by CMC	N/A	N/A
Methods Validation	Will be requested	n/a	The package will need to be updated with product specifications and analytical methods and validation data.
ODS/DMEPA	Properitory name granted.	16-Nov-2011	Jibril Abdus-Samad, PharmD
EA	Claim for categorical exclusion is acceptable	Date of this review.	Ravindra K. Kasliwal, Ph.D.

Chemistry Assessment Section

The Chemistry Review for NDA 202207

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is **not approval** for chemistry, manufacturing and controls (CMC) under section 505 of the Act. The reasons for not approval are CMC deficiencies (listed at the end of review) and withhold recommendation on manufacturing facilities from the Office of Compliance.

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

1. Recommend that the company provide a phase 4 commitment to provide 12 month long term and 6 month accelerated stability data and analysis using the new methods and updated specifications on first three production, conformance or commercial lots (reflective of commercial manufacturer). These lots should be manufactured using different lots of Tilmanocept drug substance. This commitment should be completed within 15 months of approval of this drug product.

2. Recommend that the company provide a phase 4 commitment to develop a method to quantitate (b) (4) in Lymphoseek powder vial and radiolabled drug product as part of the drug product release and stability testing program. This should be completed within 12 months of approval of this drug product.

II. Summary of Chemistry Assessments

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

Technetium Tc 99m Tilmanocept binds to receptors on mannose-binding proteins (MBP). Tilmanocept (b) (4) has a dextran (C-10) backbone conjugated with a linker moiety (an amine terminated "leash") that is subsequently coupled with Diethylenetriamine pentaacetic acid (DTPA) and mannose moieties. The mannose acts as a substrate for the receptor on MBP and the DTPA serves as a chelating agent for radiolabeling with Technetium Tc99m.

Since Tilmanocept has a dextran backbone, it has a molecular weight distribution (b) (4) carry the amine leash; of those leashes, 3-8 are conjugated to DTPA, 12-20 are conjugated to mannose and 0-17 remain as the free amine. The calculated average molecular weight of tilmanocept will range from 15,281 to 23,454. Tilmanocept is an off-white to buff colored powder that is moderately hygroscopic, very water soluble, and insoluble in alcohol. The pH of a 1% solution of Tilmanocept is ≈ 9. Tilmanocept has been observed to degrade only at extreme pH conditions. The degradation is time and temperature dependent. (b) (4).

The drug product (trademark: Lymphoseek®) will be supplied as "kit" containing a sterile lyophilized preparation of Tilmanocept, 0.25 mg (labeled as Tilmanocept Powder for Injection) and co-packaged sterile buffer saline diluent (labeled as DILUENT for Lymphoseek). Tilmanocept Powder vial contains non-radioactive ingredients necessary to produce technetium Tc 99m tilmanocept after radiolabeling with technetium Tc 99m solution obtained from a commercially available generator at the clinical site of use. The Tilmanocept powder vial contains sterile, non-pyrogenic, white to off-white powder, of a mixture of 250 mcg (0.25 mg) of tilmanocept, 20 mg trehalose dihydrate, 0.5 mg glycine, 0.5 mg sodium ascorbate, and 0.075 mg, stannous chloride dihydrate. The contents of the vial are

lyophilized and stored under nitrogen. The DILUENT for Lymphoseek contains 4.5 mL sterile buffered saline consisting of 0.04% (w/v) potassium phosphate, 0.11% (w/v) sodium phosphate (heptahydrate), 0.50% (w/v) sodium chloride, and 0.40% (w/v) phenol. The pH is 6.8 – 7.2.

The lyophilized formulation provides [redacted] (b) (4) lyophilized cake, allowing for quick reconstitution with Sodium Pertechnetate in saline to produce a clear injection solution. Each Tilmanocept powder vial can be radiolabeled with 2.5 – 10 mCi (q.s. 0.35 – 0.7 mL) of sodium pertechnetate solution. The formulation contains [redacted] (b) (4)

The pH of Lymphoseek powder vial is [redacted] (b) (4). The diluent is provided to [redacted] (b) (4) which is considered suitable for parenteral products.

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

Lymphoseek® (technetium Tc 99m tilmanocept) injection is indicated for intraoperative localization of tumor-draining lymph nodes using a handheld gamma detection probe in patients with breast cancer or melanoma. Prior to administration to the patient, the Nuclear Pharmacy will prepare the injection by taking one lyophilized powder vial and radiolabeling with an amount of radioactivity as Sodium Pertechnetate Tc 99m Injection in isotonic saline. After the prescribed time for the radiolabeling reaction ([redacted] (b) (4) the vial is brought to the prescribed volume using one of the accompanying diluent, Sterile Buffered Saline. It is then QC tested using Instant Thin Layer Chromatography (ITLC) to ensure that the raiochemcial purity is ≥ 90%, and drawn into syringe(s) according to the Physician's order. The Technetium Tc 99m Lymphoseek® Injection is typically administered to patients within a few minutes to a few hours following preparation. Because of the short half-life of the radionuclide and the mode of production, the radiolabeled drug product has a shelf life of six (?) hours.

The patient mass dose in every case is 50 µg. The volume, number of injections and amount of radiation will vary depending on the Physician's orders and the type and time of the scheduled surgery. The maximum reconstitution volume is 5.0 mL. Following lymph node mapping protocol is used.

- Use a handheld gamma counter (represented by any FDA-cleared handheld gamma detection probe) to identify nodes localizing Technetium Tc 99m Lymphoseek Injection. Measure background counts from tissue at least 20 centimeters distal to the injection site. Use the background radioactivity counts plus three standard deviations from the mean background count level (i.e., the three-sigma rule representing >99.7% probable difference from background) as the threshold for positive localization of Technetium Tc 99m Lymphoseek Injection.
- All lymphatic mapping agents use elements of the lymphatic system for distribution. The lymph node localization of Technetium Tc 99m Lymphoseek Injection is dependent upon its binding to reticuloendothelial cells within lymph nodes. Based on clinical studies, the localization and degree of localization (ability to detect multiple nodes with potential anatomic nexuses to the tumor bed) of Technetium Tc 99m Lymphoseek Injection is not dependent on the radiopharmaceutical injection technique. The use of Technetium Tc 99m Lymphoseek Injection is intended to complement palpation, visual inspection, and other procedures important to lymph node localization. Intraoperative lymphatic mapping by gamma detection should be initiated no sooner than [redacted] (b) (4) post-injection and within [redacted] (b) (4) of administration of Technetium Tc 99m Lymphoseek Injection.

C. Basis for Not-Approval Recommendation

The application is not approval because of the following issues:

1. The analytical method [redacted] used for the identification and quantitation (assay) of Tilmancept in Lymphoseek drug product is not suitable for the quantitation of tilmanocept in Lymphoseek drug product. In the method the [redacted] and therefore the assay (potency) results are not reliable. Therefore, the potency data in the NDA (release and stability) can not be relied upon.

2. The supplied in-use radiolabeled product data do not support the proposed 6 hour shelf life for the radiolabeled product.

3. The Office of Compliance (see EES report dated 25-Apr-2012) has recommended withhold from approval for the manufacturing facilities. The basis for their recommendation is:

    a. Multiple significant CGMP deficiencies in [redacted] manufactures and tests the Tilmanocept drug substance and will be performing these activities for the commercial product as well. The site currently has withhold recommendation.

    b. CGMP deficiencies in the facilities of [redacted] manufactures (lyophilized sterile fill product) the finished drug product for Navidea and will manufacture the commercial product as well. The site currently has withhold recommendation.

    c. cGMP and potency method performance deficiencies in [redacted] has developed the analytical methods and conducts release and stability testing on finished drug product. [redacted] will perform these activities for the commercial product as well. The site currently has withhold recommendation.

    Additionally, issues arising from a change in the potency method are listed under "Deficiencies to be communicated" at the end of this review. These will also need to be satisfactorily addressed prior to any approval action.

III. Administrative

A. Reviewer's Signature

Ravindra K Kasliwal, Ph.D.

B. Endorsement Block

Chemist - Name/Date: Ravindra K. Kasliwal/ See DARRTS
Chemistry Branch Chief - Name/Date: Ali Al-Hakim, Ph.D./ See DARRTS
Project Manager - Name/Date: Alberta E. Davis-Warren/ See DARRTS

C. CC Block: See DARRTS

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/s/

RAVINDRA K KASLIWAL
07/19/2012

ERIC P DUFFY
07/19/2012

Initial Quality Assessment (IQA)
For
Division of New Drug Quality Assessment III, Branch VII
Office of New Drug Quality Assessment

OND Division: DMIP
NDA: 202207
Applicant: Neoprobe Corporation
425 Metro Place North, Suite 300
Dublin, Ohio 43017
(Responsible Official: Rodger Brown, Vice President, RA/QA; phone 614-793-7500, # 142)

PDUFA: TBD
Trademark: Lymphoseek
Established: Kit for the Preparation of Technetium Tc 99m Tilmanocept for Injection
Dosage Form: Sterile solution
Route of Administration: Intradermal, subcutaneous, subareolar, or peritumoral injection
Indication: (b) (4)

CMC Lead: Eldon E. Leutzinger, Ph.D.

ONDQA Fileability YES (X) NO

Comments for 74-Day Letter: None at this time – will await review by primary reviewer

Summary and Critical Issues:

A. Summary

DRUG PRODUCT

Lymphoseek is a lyophilized vial ("cold" kit) that after radiolabeling with Sodium Pertechnetate Tc 99m Injection produces Technetium Tc 99m Tilmanocept (see review section for Drug Substance). **Each "cold" kit (pharmacy package) consists of**:

5 Single-use lyophilized vials of powder (Tilmanocept + (b) (4) + excipients) Composition (Section 3.2.P.1.2) – see Table 1, review page 2 5 Vials of diluent (Sterile Buffered Saline) Composition (Section 3.2.P.1.4) – see Table 2, review page 3

The **lyophilized vial containing Tilmanocept** is supplied in a [redacted] Vial (USP/Ph.Eur., certified Type 1 glass) with a [redacted] Stopper USP/Ph.Eur certified. The stopper is sealed to the vial with [redacted] The composition of the lyophilized vials is shown as follows, reproduced from Section 3.2.P.1.2.

Table 1. Lymphoseek® (Tilmanocept) 0.25 mg (Lyophilized Vial)

Component	Amount per vial (mg)	Function	Quality Standard
Tilmanocept	0.25	Drug Substance	Company Standard
Glycine	0.5	[redacted]	USP, Ph. Eur.
Sodium Ascorbate	0.5		USP, Ph. Eur.
Trehalose, Dihydrate	20		NF
Stannous Chloride, Dihydrate	0.075		NF, Ph. Eur.
[redacted]	[redacted]		NF, Ph. Eur.
			NF, Ph. Eur.
Nitrogen			NF, Ph. Eur.
Water For Injection	*		USP, Ph. Eur.

* Removed during processing

Section 3.2.P.2.2.1 contains a description of the development of this formulation.

Tilmanocept has the following chemical structure:

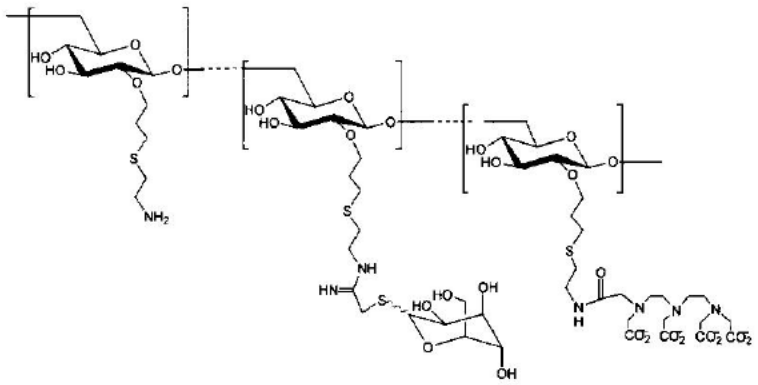

Figure 1. Tilmanocept Structural Formula (Relative Stereochemistry)

Its chemical name is Dextran, 3[(2-aminoethyl)thio]propyl 17-carboxy-10,13,16-tris(carboxymethyl)-8-oxo-4-thia-7,10,13,16-tetraazaheptadec—1yl-3-[[2-[[1-imino-2-(D-mannopyranosylthio)ethyl]amino]ethyl]thio]propyl ether. A shorter name is provided by the applicant as "diethylenetriaminepentaacetic acid mannosyl dextran," or

just DTPA Mannosyl Dextran (= Lymphoseek Ligand), CAS RN 1185986-76-8. Tilmanocept is an off-white to buff-colored powder. It is very soluble in water, but insoluble in alcohol. Tilmanocept is moderately hygroscopic. Nothing is known about polymorphism, since it has not been so investigated. It possesses 5 asymmetric centers

(b) (4)

The **diluent (Sterile Buffered Saline)** is contained in a glass vial, (b) (4) and has a DMF (b) (4) a letter of authorization is provided for access to the DMF. They say that each lot of diluent will be released by Neoprobe or their contract manufacturer (b) (4) based on the release COA provided by (b) (4) prior to co-packaging with Lymphoseek. The diluent to be co-packaged with Lymphoseek is the same as was used in the Phase 2 and Phase 3 clinical studies – supplier also the same. The composition of the diluent is as follows, as reproduced from Section 3.2.P.1.4:

Table 2. Components and Composition Buffered Saline

Component	Amount per unit (%)	Function
Potassium Phosphate	0.04	(b) (4)
Sodium Phosphate · $7H_2O$	0.11	
Sodium Chloride	0.5	
Phenol	0.4	
		(b) (4)

During radiolabeling, the DTPA end in the chain (Figure 1) complexes wit (b) (4) From the package insert, radiolabeling

consists of adding 2.5 – 10 mCi of [redacted] (b) (4) Sodium Pertechnetate Tc 99m Injection in approximately 0.35 to 0.70 mL to a Lymphoseek lyophilized vial, gently swirled and allowed to stand for [redacted] (b) (4) Diluent is next added to bring the volume contents to 5.0 mL. The vial is then assayed and checked for radiochemical purity.

COMMENTS:
Because the Kit for the Preparation of Technetium Tc 99m Tilmanocept for Injection is a "cold" kit, i.e., it requires reconstitution (radiolabeling) with Sodium Pertechnetate Tc 99m Injection before it can be used for patient administration. So, there is effectively two drug products, one prior to radiolabeling ("cold kit") and one following radiolabeling ("radiolabeled kit"). Since the latter pertains to the Drug Substance, further discussion of this point is delayed until the next section on Drug Product. However, the recognition of this nuance for radiopharmaceutical kits is important, since it bears on what should be and what does not need to be inspected for CGMP's.

Drug Product (finished "cold" kit) is manufactured by [redacted] (b) (4) product inspection, AQL testing, packaging and labeling by the same firm, but at facility with address of [redacted] (b) (4)

The manufacture of the Kit for Preparation of Technetium Tc 99m Tilmanocept for Injection essentially follows what is typical for any other radiopharmaceutical kit, the most critical element of which is establishing conditions in the kit [redacted] (b) (4) A flow diagram occurs at the end of this section (3.2.P.3.3.10). I have examined these sections and have no initial comments, and am leaving this to a more detailed review by the primary reviewer.

There are specifications for release of manufactured Kit for the Preparation of Technetium Tc 99m Tilmanocept for Injection, found in Table 1 (Section 3.2.P.5.1), for the Diluent (Buffered Saline) in Table 2 (same section). On a cursory examination, I have not found anything that jumped out at me, and am leaving these specifications for more detailed review by the primary reviewer.

Stability:
There is a reasonably good summary of the stability studies, batches in the study and data in Section 3.2.P.8.3. There is a lot of information provided in this section, and I do not intend to make any detailed discussion of it within this initial review (IQA). They have provided data for 3 primary batches of the Kit for Preparation of Tchnetium Tc 99m Tilmanocept for Injection (Lymphoseek) in the container closure system intended for

marketing [redacted] (b) (4)

12 months for Lot NMK001, 18 months for Lot NMK002, 12 months for Lot NMK003 at 25^0C/60%RH, where the testing at initial and 3 months is at [redacted] (b) (4) and 6 months / beyond is at [redacted] (b) (4) There are data for all 3 of these batches for 6 months at 40^0C/75% RH – some of the testing is done at [redacted] (b) (4) and some at [redacted] (b) (4). There are some other data that I will not discuss here. Tests and stability specifications are described in this section. I have not examined this body of stability data in great detail, but I have not seen anything too serious in its initial review (IQA); I am leaving this up to the primary reviewer, but the necessary body of data appears to be in place for filing of the NDA.

DRUG SUBSTANCE

During the radiolabeling reaction, all 5 of the carboxylic groups and the 3 nitrogen atoms in the DTPA backbone coordinate with ^{99m}Tc(IV) to form the following complex (Drug Substance):

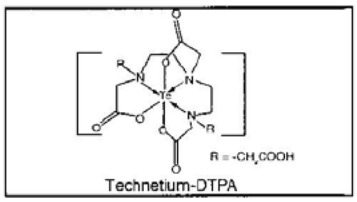

Figure 2. Possible Structure of Technetium Tc 99m-DTPA Complex

[redacted] (b) (4)

(b) (4)

[redacted] I am going to designate the issue for evidence of structure for the complex as **Critical Issue #8**. But, understand, although I am identifying it as such, it is not possess the same level of criticality as the other Critical Issues (later in this review).

Now, reference to the above complex, we are talking about two different entities. The first of these is Tilmanocept, the ligand that binds to ^{99m}Tc(IV). Since this ligand is also a compound in the following sequence, it is an immediate "precursor" to the above complex. There is no drug substance guidance at this moment. For Drug Substance, we can go to the regulations. For a definition of Final Intermediate, we must go to the following guidance:

[Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances, February 1987]

This guidance also contains a definition of Drug Substance, which is essentially that defined in the regulations. Tilmanocept (ligand, precursor) is a final intermediate, as inferred from the definition in the above indicated guidance - the "last compound synthesized before the reaction [radiolabeling] that produces the new drug substance." But, the Drug Substance is the above complex (^{99m}Tc-labeled Tilmanocept), or "active moiety," by 21 CFR 314.108(a). This is the entity that accounts for the biodistribution of radioactivity following administration of the radiolabeled kit. However, the Kit for Preparation of Technetium Tc 99m Tilmanocept for Injection is considered a finished pharmaceutical in of itself, and will be stored in the nuclear pharmacy (as any other pharmaceutical) until needed. Also, note that the NDA refers to (b) (4) as the drug substance manufacturer (so, we are well set-up to request inspection of this site).

The manufacturer of Tilmanocept is (b) (4)

The synthesis of Tilmanocept is described in Section 3.2.S.2.2. There are [redacted] (b) (4) steps [redacted] (b) (4) starting out with [redacted] (b) (4) Each of these Steps are discussed in the above indicated section. I have made a cursor examination of each of these steps, and have not identified anything of obvious concern with what they have provided [redacted] (b) (4) – that being left to the very end for the intact molecule of Tilmanocept. This will again be discussed under Critical Issues. There are specifications for Tilmanocept, and these are presented in their Table 1 (Section 3.2.S.4.1). I am going to leave most of this to the primary reviewer, but will mention one or two items in the specifications that might need some additional examination (see Critical Issues).

Stability (Tilmanocept):
They have 3 primary stability batches (commercial scale; [redacted] (b) (4)), packaged in HDPE bottles, with 24 months of data at 25 C ± 2 C and 60 ± 5% relative humidity, and 6 months of data at 40^0C ± 2^0C and 75 ± 5% relative humidity (Section 3.2.S.7.3, as well as 3.2.S.7.1). There are also data for 2 validation batches included in the section. I have not seen anything particularly concerning, based on a very cursory examination of this data. It, of course, must be examined in greater detail, and this I am leaving up to the primary reviewer.

B. Critical Issues for Review

[redacted] (b) (4)

3 pages have been Withheld in Full as b4 immediately following this page

Filing Summary:

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		All sites for manufacture of Lymphoseek & Tilmanocept (Section 3.2.P.3.1.1) .
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		
8	Does the section contain controls for the drug product?	X		
9	Has stability data and analysis been provided to support the requested expiration date?	X		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		To my knowledge, based on the listed correspondence provided in the NDA.
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		All labels.
13	Has an investigational formulations section been provided?	X		
14	Is there a Methods Validation package?	X		As qualified – within the section for analytical methods
15	Is a separate Microbiological section included?	X		As qualified – enclosed within the manufacturing section
16	Have all consults been identified and initiated?	X		Actually, not a consult, but rather an independent review assignment. John Metcalf is the assigned microbiology reviewer.

COMMENTS:
All the sites for manufacture of Lymphoseek are indicated to be ready for inspection (Section 3.2 P.3.1.1), as indicated in the above table.

Manufacturers:
In the following tables (from Form 356) are listed the facilities for manufacture of Tilmanocept and product (Kit for the Preparation of Technetium Tc 99m Tilmanocept for Injection), and the several analytical testing laboratories. See the next review page.

356h Attachment – Establishment Information

Role	Company	Address	FDA Registration Number	FEI Number	Responsibility	Name of Contact Person	Telephone No.
NDA Sponsor	Neoprobe Corporation Inc	425 Metro Place North Suite 300 Dublin, OH 43017			Quality Assurance of the drug product, release of the drug product to clinical studies.	Rodger Brown	(614) 822-2342
API Manufacturer	(b) (4)						
API Laboratory Contractor							
API Laboratory Contractor							
Product Laboratory Contractor							

356h Attachment – Establishment Information

Role	Company	Address	FDA Registration Number	FEI Number	Responsibility	Name of Contact Person	Telephone No.
Product Laboratory Contractor	(b) (4)						
Product Laboratory Contractor							
Product Laboratory Contractor							
Product Laboratory Contractor							

356h Attachment – Establishment Information

Role	Company	Address	FDA Registration Number	FEI Number	Responsibility	Name of Contact Person	Telephone No.
Production Site	(b) (4)						

COMMENTS:
Information on the manufacturers appears to be complete.

Drug Master Files
There are no DMF's described in the application.

DMF Number	Holder	Description	LOA Included	Status
[redacted] (b) (4)			Yes	--------
			Yes	--------
			Yes	--------
			Yes	--------
			Yes	--------

* Their LOA refers to [redacted] (b) (4). But, also note in the list of establishment information [redacted] (b) (4) is listed as the active ingredient manufacturer. As far as I know, each of these DMF's (unless it would be, e.g., [redacted] (b) (4)) will need to be reviewed in relation to this NDA.

Labeling:
As indicated in the Filing Summary, there is draft labeling (not only for the package insert, but also for vials and cartons). I am leaving these to the primary reviewer to address.

CMC Lead: Eldon E. Leutzinger, Ph.D. Date: 09/01/2011
Division of New Drug Quality Assessment III, Branch VII

Branch Chief: Ali Al Hakim, Ph.D.
Division of New Drug Quality Assessment III, Branch VII

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

/s/

ELDON E LEUTZINGER
09/01/2011

ALI H AL HAKIM
09/01/2011

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 202207/000	**Sponsor:**	NAVIDEA BIOPHARMS
Code:	160		425 METRO PL NORTH STE 450
Priority:	1		DUBLIN, OH 430171367
Stamp Date:	10-AUG-2011	**Brand Name:**	LYMPHOSEEK
PDUFA Date:	30-APR-2013	**Estab. Name:**	
Action Goal:		**Generic Name:**	Tilmanocept
District Goal:	01-MAR-2013	**Product Number; Dosage Form; Ingredient; Strengths**	
		001; POWDER, FOR INJECTION SOLUTION; TILMANOCEPT; .25MG	

FDA Contacts:	Y. LIU	Project Manager	3017961926
	R. KASLIWAL	Review Chemist	3017961386
	E. LEUTZINGER	Team Leader	3017961399

Overall Recommendation:	ACCEPTABLE	on 13-FEB-2013	by T. SHARP	()	3017963208
	PENDING	on 12-FEB-2013	by EES_PROD		
	PENDING	on 12-FEB-2013	by EES_PROD		
	WITHHOLD	on 30-AUG-2012	by D. SMITH	(HFD-323)	3017965321
	PENDING	on 09-AUG-2012	by EES_PROD		
	PENDING	on 18-JUL-2012	by EES_PROD		
	WITHHOLD	on 25-APR-2012	by EES_PROD		
	WITHHOLD	on 18-APR-2012	by EES_PROD		
	PENDING	on 18-APR-2012	by EES_PROD		
	WITHHOLD	on 18-APR-2012	by EES_PROD		
	PENDING	on 14-DEC-2011	by EES_PROD		
	PENDING	on 17-NOV-2011	by EES_PROD		
	PENDING	on 16-NOV-2011	by EES_PROD		
	PENDING	on 11-OCT-2011	by EES_PROD		
	PENDING	on 27-SEP-2011	by EES_PROD		

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	(b) (4)		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: (b) (4)

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: **CFN:** (b) (4) (b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: (b) (4)

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** (b) (4) (b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: (b) (4)

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **CFN:** **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: (b) (4)

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: (b) (4)

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: (b) (4)

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: SMALL VOLUME PARENTERAL, LYOPHILIZED **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: (b) (4)

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: (b) (4)

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: (b) (4)

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

plication:	NDA 202207/000	**Sponsor:**	NAVIDEA BIOPHARMS
]. C	160		425 METRO PL NORTH STE 450
prity.	1		DUBLIN, OH 43017
mp Date:	10-AUG-2011	**Brand Name:**	LYMPHOSEEK
JFA Date:	10-SEP-2012	**Estab. Name:**	
ion Goal:		**Generic Name:**	Tilmanocept
trict Goal:	11-APR-2012	**Product Number; Dosage Form; Ingredient; Strengths**	
		001; POWDER, FOR INJECTION SOLUTION; TILMANOCEPT; .25MG	

A Contacts:	Y. LIU	Project Manager	3017961926
	R. KASLIWAL	Review Chemist	3017961386
	E. LEUTZINGER	Team Leader	3017961399

erall Recommendation:	WITHHOLD	on 30-AUG-2012	by D. SMITH	(HFD-323)	3017965321
	PENDING	on 09-AUG-2012	by EES_PROD		
	PENDING	on 18-JUL-2012	by EES_PROD		
	WITHHOLD	on 25-APR-2012	by EES_PROD		
	WITHHOLD	on 18-APR-2012	by EES_PROD		
	PENDING	on 18-APR-2012	by EES_PROD		
	WITHHOLD	on 18-APR-2012	by EES_PROD		
	PENDING	on 14-DEC-2011	by EES_PROD		
	PENDING	on 17-NOV-2011	by EES_PROD		
	PENDING	on 16-NOV-2011	by EES_PROD		
	PENDING	on 11-OCT-2011	by EES_PROD		
	PENDING	on 27-SEP-2011	by EES_PROD		

ablishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
F No:		**AADA:**	
sponsibilities:	DRUG SUBSTANCE STABILITY TESTER		
file:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
t Milestone:	OC RECOMMENDATION		
estone Date:	(b) (4)		
cision:	ACCEPTABLE		
ason:	DISTRICT RECOMMENDATION		

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

ablishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

F No: **AADA:**

ponsibilities: FINISHED DOSAGE RELEASE TESTER

file: CONTROL TESTING LABORATORY **OAI Status:** NONE

t Milestone: OC RECOMMENDATION

estone Date: (b) (4)

cision: ACCEPTABLE

ason: BASED ON PROFILE

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ablishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

(b) (4)

F No: **AADA:**

ponsibilities: FINISHED DOSAGE RELEASE TESTER

file: CONTROL TESTING LABORATORY **OAI Status:** NONE

t Milestone: OC RECOMMENDATION

estone Date: (b) (4)

cisi ACCEPTABLE

ason: DISTRICT RECOMMENDATION

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ablishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

F No: **AADA:**

ponsibilities: FINISHED DOSAGE RELEASE TESTER

file: CONTROL TESTING LABORATORY **OAI Status:** NONE

t Milestone: OC RECOMMENDATION

estone Date: (b) (4)

cision: ACCEPTABLE

ason: DISTRICT RECOMMENDATION

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

ablishment: CFN: FEI: (b) (4)

(b) (4)

F No: AADA:

ponsibilities: FINISHED DOSAGE MANUFACTURER

file: STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS OAI Status: NONE

t Milestone: OC RECOMMENDATION

estone Date: (b) (4)

ision: ACCEPTABLE

ison: DISTRICT RECOMMENDATION

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ablishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

F No: AADA:

ponsibilities: FINISHED DOSAGE RELEASE TESTER

file: CONTROL TESTING LABORATORY OAI Status: NONE

t Milestone: OC RECOMMENDATION

est Date: (b) (4)

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ablishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

F No: AADA:

ponsibilities: FINISHED DOSAGE RELEASE TESTER

file: CONTROL TESTING LABORATORY OAI Status: NONE

t Milestone: OC RECOMMENDATION

estone Date: (b) (4)

ision: ACCEPTABLE

ison: DISTRICT RECOMMENDATION

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

ablishment:	CFN: (b) (4)	FEI: (b) (4)	
	(b) (4)		
F No:		AADA:	
ponsibilities:	FINISHED DOSAGE MANUFACTURER		
file:	SMALL VOLUME PARENTERAL, LYOPHILIZED	OAI Status:	NONE
t Milestone:	OC RECOMMENDATION		
estone Date:	(b) (4)		
ision:	WITHHOLD		
ason:	DISTRICT RECOMMENDATION EIR REVIEW-CONCUR W/DISTRICT		

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

ADMIN CLOSURE-IGNORE RECCOMEND

ablishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

F No: **AADA:**

ponsibilities: DRUG SUBSTANCE STABILITY TESTER

file: CONTROL TESTING LABORATORY **OAI Status:** NONE

t Milestone: OC RECOMMENDATION

estone Date: (b) (4)

cision: ACCEPTABLE

ason: BASED ON PROFILE

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ablishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

F No: **AADA:**

ponsibilities: DRUG SUBSTANCE MANUFACTURER

file: (b) (4) **OAI Status:** NONE

t Milestone: OC RECOMMENDATION

estone Date: (b) (4)

cision: WITHHOLD

ason: DISTRICT RECOMMENDATION
EIR REVIEW-CONCUR W/DISTRICT
