

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202207Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 202207

SUPPL #

HFD # 160

Trade Name Lymphoseek

Generic Name Tilmanocept

Applicant Name Navidea Biopharmaceuticals

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Five

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====

Name of person completing form: Alberta Davis-Warren
Title: Regulatory Health Project Manager
Date: 2-27-13

Name of Office/Division Director signing form: ODEIV/Rafel Dwaine Rieves, M.D.
Title: Director/Division of Medical Imaging Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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
02/27/2013

RAFEL D RIEVES
02/27/2013

Navidea Biopharmaceuticals, Inc. Company Debarment Status Certification Statement

In accordance with Section 306(k) (1) of the Federal Food, Drug, and Cosmetic Act, Navidea Biopharmaceuticals, Inc. 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.

Rodger A. Brown Rodger A. Brown 15 AUG 2012
Print Name Signature Date (DDMMYYYY)

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 202207 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Lymphoseek Established/Proper Name: Tilmanocept Dosage Form: Powder for Injection		Applicant: Navidea Biopharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Alberta Davis-Warren		Division: Division of Medical Imaging Products
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A 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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>April 30, 2013</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> ██████ CR 9-10-12

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics ³</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): Radioactive Diagnostic Agent</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)</p> <p>Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Communication Plan <input type="checkbox"/> Submitted in response to a Pediatric Written Request <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required</p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<p><input type="checkbox"/> Yes, dates</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> • Office of Executive Programs (OEP) liaison has been notified of action 	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> • Press Office notified of action (by OEP) 	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> • Indicate what types (if any) of information dissemination are anticipated 	<p><input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other</p>

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
CONTENTS OF ACTION PACKAGE	
<p>❖ Copy of this Action Package Checklist⁴</p>	<p>X</p>
Officer/Employee List	
<p>❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p><input checked="" type="checkbox"/> Included</p>
Action Letters	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Action(s) and date(s) AP 3-13-13</p>
Labeling	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	<p>X</p>
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<p>X</p>
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	X
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	1-15-13, 8-7-12 , &11-16-11
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 10-21-11 <input checked="" type="checkbox"/> DMEPA 2-3-13 & 6-22-12 <input type="checkbox"/> DMPP/PLT (DRISK) <input checked="" type="checkbox"/> ODPD (DDMAC) 4-3-12 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews PMHS 4-10-12
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	RPM Filing Review 10-12-11
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte 	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC 4-11-12 If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>) 	<input checked="" type="checkbox"/> Verified, statement is acceptable

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	X
❖ Internal memoranda, telecons, etc.	X
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> [REDACTED] 10-4-10
• EOP2 meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> [REDACTED] 10-24-07
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> [REDACTED] 3-11-13 & 9-7-12
Division Director Summary Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> [REDACTED] 3-5-13 & 8-25-12
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> [REDACTED] 7-30-12
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	See CDTL Review dated 7-30-12
• Clinical review(s) (<i>indicate date for each review</i>)	2-26-13, 8-27-12, & 7-6-12
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See Clinical Review dated 8-27-12
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> [REDACTED] DOP2 3-15-12, PMHS 12-21-11 & 4-3-12
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)	
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input checked="" type="checkbox"/> [REDACTED] 2-9-12

⁶ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> [REDACTED] Co-signed primary review dated 7-25-12
Statistical Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> [REDACTED] 7-25-12
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> [REDACTED] Co-signed primary review dated 7-12-12
Clinical Pharmacology review(s) (indicate date for each review)	<input checked="" type="checkbox"/> [REDACTED] 7-12-12
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> [REDACTED] 7-26-12
• Supervisory Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> [REDACTED] Co-signed primary review dated 6-27-12
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input checked="" type="checkbox"/> [REDACTED] 6-27-12
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> [REDACTED] 2-26-13 & 9-5-12
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	<input checked="" type="checkbox"/> [REDACTED] 2-26-13, 8-27-12, 7-20-12, 7-19-12
❖ Microbiology Reviews	<input checked="" type="checkbox"/> [REDACTED] 4-9-12
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input checked="" type="checkbox"/> None

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	See CMC review dated 2-26-13
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷</i>)	Date completed: 2-13-13 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input checked="" type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
- (3) **Or** 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) **And** 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.
- (3) **And** 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) **Or** 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.
- (3) **Or** 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 ODE's ADRA.

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/s/

ALBERTA E DAVIS WARREN
03/13/2013

Davis-Warren, Alberta E

From: Davis-Warren, Alberta E
Sent: Friday, February 08, 2013 1:35 PM
To: 'Brown, Rodger'
Cc: Regan, Bill; regulatoryaffairs
Subject: NDA 202207 Lymphoseek poster and package insert

Dear Mr. Brown,

Attached are comments regarding the Lymphoseek poster and FDA's edits to the Lymphoseek package insert. Please provide a response to the comments and edits by COB, Friday February 15, 2013. Please also submit to the NDA a revised poster and a revised package insert.



NDA 202207
Feb2013 poster ...



NDA 202207
Feb2013 FDA e...

Please contact me if you have any questions.

Thank you,

Alberta

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
301-796-3908 office
301-796-9849 fax
Alberta.Davis-Warren@fda.hhs.gov

FDA does not ensure the security of email communications. If you desire to communicate by secure email, please establish a secure email channel by contacting SecureEmail@fda.hhs.gov.

NDA 202207: Lymphoseek

CMC Comments regarding preparation instructions poster:



DMEPA's comments regarding preparation instructions poster:



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

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/s/

ALBERTA E DAVIS WARREN
02/08/2013



NDA 202207

GENERAL ADVICE

Navidea Biopharmaceuticals, Inc
Attention: Rodger A. Brown
Vice President, Global Regulatory Affairs and Quality Operations
425 Metro Place North
Suite 450
Dublin, Ohio 43017

Dear Mr. Brown:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lymphoseek, (Technetium Tc 99m Tilmanocept) Injection.

We also refer to your December 4, 2012, submission that contained references to marketing applications where an inspection was either waived or deferred to a post-approval requirement during the drug review process. You cited these applications as setting a precedent for post-approval inspection of manufacturing facilities.

We have reviewed the referenced material and have the following comments:

We appreciate your communication about the review processes for the marketing applications cited as precedents. We do not agree that the inspectional scenarios with these other applications are comparable to your application. That is, the cited experience does not negate the need for a pre-approval inspection of your drug's manufacturing facility. We described our perspective to you in a conversation on November 26, 2012.

We appreciate the opportunity to examine the referenced marketing application experience. We will contact you if additional information is needed during this review cycle.

If you have any questions, call Alberta Davis-Warren, Regulatory Project Manager, at (301) 796-3908.

Sincerely,

{See appended electronic signature page}

Rafel Dwaine Rieves, M.D.
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

RAFEL D RIEVES
12/12/2012

MEMORANDUM OF MEETING

DATE: November 26, 2012

APPLICATION NUMBER: NDA 202207 Lymphoseek

BETWEEN: **Navidea Biopharmaceuticals, Inc.:**
Mark Pykett, V.M.D., Ph.D., Navidea CEO
William J Regan, SVP Global Regulatory Strategy
Thomas Tulip, Ph.D., EVP, President & CBO
Rodger Brown, VP Global Regulatory Operations and Quality Assurance
Dave Casebier, Ph.D., VP CMC
George Mills, M.D., Navidea Regulatory Consultant

(b) (4)

AND

FDA

LCDR Tara Goen, Branch Chief (acting), OC, OMPQ, DGMPA

(b) (4)

Eric Duffy, Ph.D., Director, DNQAIII,
Eldon Leutzinger, Ph.D., CMC Team Leader, DNQAIII
Charles Ganley, M.D., Director, ODEIV
Dwayne Rieves, M.D., Director, DMIP
Libero Marzella, M.D., Ph.D., Deputy Director, DMIP
Alex Gorovets, M.D., Clinical Team Leader, DMIP
Alberta Davis-Warren, Regulatory Health Project Manager, DMIP

SUBJECT: Re-Inspection of (b) (4)

HISTORY: Navidea Biopharmaceuticals, Inc. requested a teleconference with LCDR Tara Goen to discuss the timing for the planned FDA inspection at (b) (4). Navidea also wanted to understand the timing for communicating inspection results to the Center and the expected cycle time to recommend approval if inspection results are satisfactory. Finally, Navidea requested FDA to allocate resources from the Center or another district office to conduct the inspection if the inspection cannot occur in the short term because of the (b) (4) District Office resource limitations. Prior to the meeting Navidea provided correspondence to assist in the discussion in today's teleconference (see attached).

TODAY'S Meeting:

Navidea started the discussion summarizing the correspondence they sent to the FDA on November 26, 2012 (see attached). Navidea then asked if it is possible to approve the application in advance of the re-inspection with the commitment from Navidea that Navidea will not market the product before the inspection is satisfactorily completed.

FDA stated that before discussing Navidea's proposal, the agency wanted to clarify a couple of items. 1) During the first review cycle it was not possible to complete the evaluation of the potency assay transfer to (b) (4) before the PDUFA date; the potency assay was transferred to (b) (4) late in the review cycle so this evaluation now has to be completed. 2) Regarding the current review cycle, the rescheduling of the inspection from November to January was not due to district resource constraints.

In regards to Navidea's proposal to have the NDA approved but marketing contingent upon inspection results, FDA disagreed with this plan. FDA stated that the potency assay transfer and associated data needs to be verified by performing the on-site inspection before recommending approval of the application.

Navidea stated that they sent extensive documentation of the potency method to the (b) (4) District office and thought providing the documents in advance was a part of the inspection process. Navidea asked why the facility had to be inspected. FDA replied that sending the information to (b) (4) made the inspection of the site more efficient however it did not replace the need for onsite inspection. FDA also stated that review of method validation goes beyond the validation report. An onsite inspection would allow for FDA to verify the data presented in the report by reviewing raw data, including chromatograms and laboratory notebooks.

Navidea stated that since a single inspection issue appears to prevent approval, they could not understand why the NDA could not be approved in advance of the re-inspection with a commitment to not market the product until the inspection was complete. FDA stated that the evaluation of facilities and associated pre-approval inspections are done prior to approval. Navidea wanted a confirmation from the Agency that the inspection will be held in January. FDA stated as of now the inspection is scheduled to be held in January. Navidea inquired about the pre-approval timing and the additional steps involved before granting approval. FDA stated that after inspection the District office has five days to provide the recommendation to CDER. CDER will then need to review the case and discuss inspectional findings with the district. In terms of the timing of approving the application if the inspection is acceptable FDA will expedite the administrative steps and most likely the action will occur prior to the PDUFA date April 30, 2013.

Alberta Davis-Warren
Regulatory Health Project Manager, DMIP

Attachment:
Navidea Correspondence

I am writing in advance of the telephonic meeting between Navidea and FDA scheduled for 16:10 EST later today, November 26, 2012, regarding NDA 202207 for Lymphoseek, a lymphatic mapping agent for breast cancer and melanoma. Navidea believes this product provides an important health benefit to patients with those cancers, and we look forward to discussing steps to take toward timely approval of Lymphoseek. To that end, this letter is intended to help focus the discussion, in order to use the allotted time most efficiently.

Navidea received a Complete Response Letter (CRL) for the Lymphoseek NDA 202207 from FDA on 10 September 2012. The CRL raises no issues regarding the safety or efficacy of Lymphoseek, which has been the subject of adequate and well-controlled clinical trials that represent more than 525 human administrations and to date have resulted in not a single drug-related significant adverse event. Similarly, the Agency has identified no concerns regarding the CMC component of the NDA. According to the CRL, the sole issue preventing approval of NDA 202207 is the cGMP compliance at the contract manufacturing organization (CMO) facilities operated by (b) (4).¹

Following receipt of the CRL, Navidea, (b) (4) have worked diligently to address the deficiencies identified to the CMOs during recent facility inspections. This work culminated in Navidea's NDA Complete Response (CR) submission to the NDA on 30 October 2012; that CR submission explained that (1) all deficiencies and Form FDA 483 observations identified by FDA inspectors had been addressed, (2) the vast majority of corrective and preventative actions (CAPAs) had been completed, and (3) we believe the CMOs are now cGMP compliant. The Agency accepted the resubmission, assigning a Class II designation, which resulted in a PDUFA date of April 30, 2013 for action on the NDA.

The Agency has communicated to Navidea that an inspection of the (b) (4) facility will be required before the NDA can be approved. It is our understanding that the primary reasons for re-inspection is to verify a new drug product method installed at (b) (4) that was not available during the original inspection and to verify cGMPs as they pertain to Lymphoseek. We believe we have addressed these FDA requirements.

First, as agreed to by the (b) (4) District Office (b) (4), they have reviewed the (b) (4) validation protocol, validation report and substantial data in support of a virtual/paper evaluation of this method, and have indicated that the method appears effective and the data appear adequate. The new drug product potency method continues to perform as expected at (b) (4), and has been employed to test release, stability and product validation studies samples at (b) (4) and continues to perform as expected. Additionally, the method validation, as well as results from the method, have been reviewed by the CDER CMC team and found acceptable.

Second, in support of general cGMP compliance at (b) (4) pertaining to Lymphoseek, (b) (4) has provided (b) (4) with the master batch record of the current Lymphoseek drug substance

¹ As the CRL states, Navidea has responded to the Agency's requested labeling revisions, the Agency has no additional requests in this regard, and FDA reserves comment on the final proposed labeling until the NDA is, in the Agency's view, otherwise adequate.

manufacturing process, demonstrating appropriate adherence to GMP's.

The CAPA Plan addressing the Form FDA 483 observations at (b) (4) has been agreed to by the (b) (4), and has been implemented in all material respects. We believe (b) (4) is cGMP compliant and ready for inspection, and has been for some time. In August the (b) (4) scheduled an inspection for the week of 5 November; just before that date, however, (b) (4) postponed the inspection, due to limited Agency resources. We understand that the inspection will not take place before early 2013, perhaps in January, although no date has yet been confirmed. We recognize the difficult choices the Agency must make in allocating resources among competing priorities, but are concerned that in this instance, the approval of Navidea will significantly and unnecessarily be delayed.

With that in mind, we would like to discuss the possibility of the Agency approving the Lymphoseek NDA in advance of the re-inspection, based on the substantial information regarding cGMP compliance at (b) (4) that FDA already has, with an Agency commitment to conduct the inspection in January 2013, and a commitment from Navidea not to launch the product before the inspection is satisfactorily completed. This would keep the Lymphoseek NDA moving forward within the context of the Agency's need to meet its myriad responsibilities.

Navidea wishes to thank the Agency in advance for its consideration and looks forward to a collaborative meeting today.

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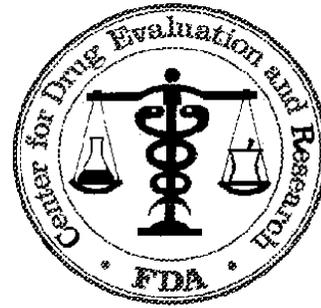
/s/

ALBERTA E DAVIS WARREN
12/21/2012

FAX

**FOOD AND DRUG ADMINISTRATION
DIVISION OF MEDICAL IMAGING PRODUCTS**

5901-B Ammendale Road
Beltsville, Maryland 20705



To: Rodger A. Brown **From:** Alberta Davis-Warren
FAX/EMAIL rbrown@navidea.com **FAX:** 301-796-9849
Phone: 614-793-7500 **Phone:** 301-796-3908
Pages, including cover sheet: 3 **Date:** November 9, 2012
RE: Information Requests for NDA 202207

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the address above by mail. Thank you.

Dear Mr. Brown:

We make reference to your New Drug Application (NDA) for Lymphoseek, submitted on October 30, 2012 under section 505(b) of the Federal Food, Drug, and Cosmetic Act. During our review of your submission, we have the following Information Requests:

In your resubmission document dated October 29, 2012, the following statement was made:

“During the Type A meeting, Navidea inquired if any changes or modifications needed to be addressed in the closed bioburden OOS investigation report, and FDA indicated no.”

The closed bioburden OOS report (PR: 160627) includes the following Preventative Action:

[REDACTED] (b) (4)

During the Type A meeting, FDA representatives voiced concerns with changing the sample [REDACTED] (b) (4) Please clarify your bioburden sampling and testing plan for Lymphoseek commercial products. It should be noted that FDA has not approved your investigation or indicated that it is accurate or complete.

Please respond to these requests by no later than **November 14, 2012 at 4:00 pm ET**. Please submit an amendment to your application with your response to the requests using the official channels. To expedite the review process, please send me a courtesy copy through e-mail (Alberta.Davis-Warren@fda.hhs.gov) or FAX (301-796-9849) no later than **November 14, 2012 at 4:00 pm ET**.

Thank you.

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
CDER, FDA

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/s/

ALBERTA E DAVIS WARREN
11/09/2012



NDA 202207

**ACKNOWLEDGE –
CLASS 2 RESPONSE**

Navidea Biopharmaceuticals, Inc
Attention: Rodger A. Brown
Vice President, Global Regulatory and Quality Operations
425 Metro Place North
Suite 450
Dublin, Ohio 43017

Dear Mr. Brown:

We acknowledge receipt on October 31, 2012, of your October 30, 2012, resubmission of your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lymphoseek, (Technetium Tc 99m Tilmanocept) Injection.

We consider this a complete, class 2 response to our September 10, 2012, action letter. Therefore, the user fee goal date is April 30, 2013.

If you have any questions, call me, at (301) 796-3908.

Sincerely,

{See appended electronic signature page}

Alberta Davis-Warren, B.S.
Regulatory Health Project Manager
Division of Medical Imaging Projects
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

ALBERTA E DAVIS WARREN
11/09/2012



NDA 202207

MEETING MINUTES

Navidea Biopharmaceuticals, Inc
Attention: Rodger A. Brown
Vice President, Global Regulatory and Quality Operations
425 Metro Place North
Suite 450
Dublin, Ohio 43017

Dear Mr. Brown:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lymphoseek.

We also refer to the meeting between representatives of your firm and the FDA on October 9, 2012. The purpose of the meeting was to address issues in the Complete Response letter pertaining to cGMP status at the two contract manufacturing organizations.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3908.

Sincerely,

{See appended electronic signature page}

Alberta Davis-Warren, B.S.
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: A
Meeting Category: Guidance

Meeting Date and Time: October 9, 2012 4 pm – 5pm ET
Meeting Location: White Oak campus Building 22 Conference room 1415

Application Number: NDA 202207
Product Name: Lymphoseek
Indication: (b) (4) localization of lymph nodes in patients with breast cancer or melanoma
Sponsor/Applicant Name: Navidea Biopharmaceuticals, Inc.

Meeting Chair: LCDR Tara Goen, Division Director (acting), OC, OMPQ, DGMPA
Meeting Recorder: Alberta Davis-Warren

FDA ATTENDEES

LCDR Tara Goen, Division Director (acting), OC, OMPQ, DGMPA
Derek Smith, Ph.D., Chemist, OC, OMPQ, DGMPA
Eric Duffy, Ph.D., Director, DNQAIII,
Eldon Leutzinger, Ph.D., CMC Team Leader, DNQAIII
John Metcalfe, Ph.D., Microbiology Reviewer, OPS (by phone)

(b) (4)

Charles Ganley, M.D., Director, ODEIV
Dwayne Rieves, M.D., Director, DMIP
Libero Marzella, M.D., Ph.D., Deputy Director, DMIP
Alex Gorovets, M.D., Clinical Team Leader, DMIP (by phone)
Brenda Ye, M.D., Medical Officer, DMIP
Lucie Yang, M.D., Ph.D., Clinical Team Leader, DMIP
Satish Misra, Ph.D., Statistical Reviewer, DBV
Alberta Davis-Warren, Regulatory Health Project Manager, DMIP

SPONSOR ATTENDEES

Navidea Biopharmaceuticals, Inc.

Mark Pykett, V.M.D., Ph.D., President and Chief Executive Officer

Thomas Tulip, Ph.D., Executive Vice President & Chief Business Officer

William (Bill) Regan, Senior Vice President, Global Regulatory Strategy

Rodger Brown, Vice President, Global Regulatory and Quality Operations

Ann Maloney, Director, Drug Development and Compliance

(b) (4)

David Casebier, Ph.D., (Navidea Consultant)

Stephen Haber, Ph.D., (Navidea Consultant)

(b) (4)

1.0 BACKGROUND

On September 10, 2012 Navidea Biopharmaceuticals Inc. received a complete response letter from FDA for NDA 202207 (Lymphoseek). In the letter, FDA informed Navidea that CDER field investigators conveyed deficiencies to (b) (4) for the lymphoseek application and that the deficiencies must be resolved before the lymphoseek application can be approved.

The purpose for today's meeting was to address issues in the Complete Response letter pertaining to cGMP status at two contract manufacturing organizations (b) (4)

We received the background packages for this meeting on September 26, 2012. We sent the preliminary responses to the sponsor on October 4, 2012.

2. DISCUSSION

After introductions of the meeting participants, FDA confirmed with the applicant that the letters of authorization the Agency received from Navidea grant permission for FDA to discuss the manufacturing facility issues regarding lymphoseek with all three parties present at the meeting today. The Applicant presented their power point presentation which provided updates and addressed the Agency's responses to the Applicant's questions.

Questions

1. Per the CRL, what is the FDA's definition of "resolution of these deficiencies"?

FDA response (10-4-12): Appropriate corrective and preventive actions need to be implemented for the significant deficiencies observed. Upon completion of these activities, the Agency may determine that there is "resolution of the deficiencies." In some cases, a re-inspection may be needed to verify the implementation and adequacy of the corrective actions. Any inspections needed would typically occur during the review of the re-submission.

Meeting Discussion (10-9-12): No Discussion

- 1a. Pending the definition of the above, which specific deficiencies must be resolved satisfactorily before approval of the application?

FDA response (10-4-12): The inspectional findings were documented on the Form FDA-483s that were issued to (b) (4) specifically:

- (b) (4) had an open investigation (b) (4) bioburden which placed the master batch record on hold.
- (b) (4) did not adequately demonstrate that the manufacturing inconsistencies observed in the first three commercial-scale batches were

resolved and that (b) (4) will be capable of robust manufacturing of tilmanocept API.

Additionally, the potency assay, which was found inadequate during a pre-approval inspection of (b) (4), was modified and moved to (b) (4) late in the first review cycle. The adequacy of the establishment with respect to the amendment will be fully evaluated during the re-submission review cycle.

Navidea Response (10-9-12):

Navidea (b) (4) have closed the bioburden investigation .

The master batch record is under change control to include preventative actions for future production.

As indicated in Slide #3, Navidea (b) (4) have taken significant actions to address all observations including implementing precise manufacturing directions thru change control to the master batch record to assure consistent manufacturing execution.

Navidea submitted the validated new potency assay on August 2, 2012. (b) (4) has successfully implemented this new assay (slide # 4) which is now in routine use.

Meeting Discussion (10-9-12): FDA stated that they reviewed the final study report from (b) (4) and that they have questions regarding the investigations. These issues will be discussed toward the end of today's meeting.

2. The CMOs have developed corrective action plans including implementation timing based upon the 483 observations.

2a. Does FDA agree that these plans fully address the observations?

2b. Does the FDA agree with the completion timing for the corrective action plans?

2a+2b FDA response (10-4-12): As stated during the September 18 t-con, your CMOs' responses and corrective action plans to address significant deficiencies generally appear adequate. It should be noted that (b) (4) bioburden testing is expected to be performed (b) (4) For significant deficiencies, the corrective actions must be implemented prior to an approval recommendation. Re-inspection(s) may be needed to verify the implementation of the actions and make final determination(s) on the adequacy of the corrections.

Navidea Response (10-9-12): In the completed bioburden investigation report and in recent communications with the Agency, Navidea indicated that it intends to rely on (b) (4) to establish bioburden control in the manufacturing process.

Navidea is planning a change to the sampling point for the bioburden test for subsequent manufacturing of Lymphoseek. Bioburden data from this sample point (b) (4) more accurately reflects the actual challenge

presented to the [REDACTED] ^{(b) (4)} than does the current testing procedure. The limit for [REDACTED] ^{(b) (4)} will be applied to this sample test result.



3. We believe all other establishments in the NDA are satisfactory and no other actions are required at this time.

3a. Does FDA agree?

FDA response (10-4-12): At this time, all other manufacturing facilities appear acceptable to support an approval recommendation for NDA 202-207. However, the CGMP compliance of a facility can change independent of the application review process. It remains the sponsor's responsibility to ensure the selection and use of appropriate contract facilities. The compliance status of each facility named in the application may be re-evaluated upon re-submission.

Meeting Discussion (10-9-12): No Discussion

4. Upon resubmission to address the CRL what will be the timing of the FDA review?

FDA response (10-4-12): This is a review issue. Upon receipt of the resubmission, the review team will determine whether it is a class I submission (2 month clock) or a class II submission (6 month clock). You will be notified once the determination has been made.

Meeting Discussion (10-9-12): No Discussion

5. (b) (4)

(b) (4) was inspected by FDA (b) (4) District Office between (b) (4) and Navidea understands that (b) (4) may be re-inspected in October. Assuming satisfactory results, will this re-inspection serve to fully address and remove the (b) (4) withhold status and close the CRL issues related to the (b) (4) facility?

FDA response (10-4-12): The inspection plan is to focus solely on Tilmanocept and supporting GMP systems. An adequate inspection outcome would satisfy (b) (4) District Office for an approval recommendation of Tilmanocept API to CDER Office of Compliance. It is important to note that this is not planned to be a full GMP inspection.

Meeting Discussion (10-9-12): FDA stated that (b) (4) is not required to manufacture a batch before resubmission. However they must be able to justify that the proposed manufacturing process is supported by scientific data/justification. (b) (4) had communicated in the response to the FDA-483 that another batch would need to be manufactured in order to meet this expectation.

Navidea questioned the difference between the process validation data required for approval of the NDA vs. distribution of commercial batches. FDA responded that the expectation for approval is robust scientific data/justification of the proposed manufacturing process. In this instance, there were serious deficiencies observed on inspection that needed to be corrected prior to an approval recommendation. Navidea stated that (b) (4) provided a protocol in response to the inspection. FDA replied that the protocol is a plan to perform further studies and is not scientific justification/data needed to justify the current manufacturing process.

Navidea asked since they have addressed the 483, can an approval be done without an inspection? FDA replied that the inspection for the initial site for the potency assay observed serious problems prior to it being transferred to (b) (4). The transfer of the potency assay was late in the review cycle and therefore unable to be covered during the first review cycle. Therefore, the potency assay will be evaluated during the resubmission.

FDA (b) (4) District Office stated that any information (b) (4) can provide to them prior to the inspection is very useful. Navidea stated that (b) (4) will be ready for inspections in November and all 7 corrections will be completed by November 5th. The issues regarding (b) (4) were addressed and this concluded (b) (4) participation in the teleconference.

The remainder of the meeting focused on issues with (b) (4).

6. (b) (4)

(b) (4) was inspected by FDA (b) (4) District Office between (b) (4) and are not aware of any re-inspection dates. Is a re-inspection of (b) (4) required for the CRL resubmission?

FDA response (10-4-12): A re-inspection of either (b) (4) is not required prior to the CRL re-submission. You may re-submit your application when your contract manufacturers have adequately addressed the significant deficiencies, including implementation of corrective actions, and are ready for re-inspection. The decision to perform an additional inspection will be made during the re-submission review cycle.

Navidea Response (10-9-12):

Navidea understands the Agency's response and has taken appropriate actions. We believe that Navidea and our CMOs have adequately addressed all significant requirements in preparation for re-submission.

Meeting Discussion (10-9-12): FDA reiterated the importance of bioburden testing. The bioburden test is an indicator of the microbiological quality of the drug solution (b) (4) High bioburden counts can lead to adulteration of the product. Microbial metabolites resultant from a high bioburden can end up in the drug product since they are capable of (b) (4). Early in the NDA review, FDA sent an information request asking Navidea why the (b) (4)

The response Navidea provided to the agency was found acceptable to the CDER microbiology team. However, the CDER microbiologist's acceptable recommendation to the CDER review team was based on the understanding that Navidea stated in the NDA that the bioburden sample would be (b) (4)

In summary, if Navidea plans to change the (b) (4) bioburden commitments, the changes need to be included in the resubmission of the NDA, and it will be reviewed.

FDA had a comment regarding the OOS report of the bioburden investigation.

(b) (4)

(b) (4)

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion

4.0 ACTION ITEMS

Navidea will be in contact with the (b) (4) District office in order to provide additional information from (b) (4) which may be helpful to evaluate. Navidea will provide (b) (4) updated master batch record to the (b) (4) District Office.

5.0 ATTACHMENTS AND HANDOUTS

Navidea Biopharmaceuticals slide presentation

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

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/s/

ALBERTA E DAVIS WARREN
11/07/2012



**Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation IV
 Division of Medical Imaging Products**

FACSIMILE TRANSMITTAL SHEET

DATE: October 4, 2012

To: Rodger A. Brown Vice President, Regulatory Affairs and Quality Assurance	From: Alberta E. Davis-Warren Regulatory Health Project Manager Alberta.Davis-Warren@fda.hhs.gov
Company: Navidea Biopharmaceuticals, Inc.	Division of Medical Imaging Products
Email: rbrown@navidea.com	Fax number: 301-796-9849
Phone number: 614-793-7500 x142	Phone number: 301-796-3908
Subject: Preliminary responses for NDA 202207 Lymphoseek Type A Meeting	

Total no. of pages including cover: 5

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-3908. Thank you.

Dear Mr. Brown,

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for October 9, 2012, 4:00 pm - 5:00 pm, White Oak Bldg. 22, Room 1415 between Navidea Biopharmaceuticals and FDA. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any

modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

**PRELIMINARY RESPONSES for October 9, 2012 Type A Meeting with
Navidea Biopharmaceuticals, Inc. 4:00 PM – 5:00 PM
(NDA 202207, Lymphoseek)**

Questions are grouped by discipline

General:

1. Per the CRL, what is the FDA's definition of "resolution of these deficiencies"?

FDA response: Appropriate corrective and preventive actions need to be implemented for the significant deficiencies observed. Upon completion of these activities, the Agency may determine that there is "resolution of the deficiencies." In some cases, a re-inspection may be needed to verify the implementation and adequacy of the corrective actions. Any inspections needed would typically occur during the review of the re-submission.

- 1a. Pending the definition of the above, which specific deficiencies must be resolved satisfactorily before approval of the application?

FDA response: The inspectional findings were documented on the Form FDA-483s that were issued to (b) (4) specifically:

- (b) (4) had an open investigation (b) (4) bioburden which placed the master batch record on hold.
- (b) (4) did not adequately demonstrate that the manufacturing inconsistencies observed in the first three commercial-scale batches were resolved and that (b) (4) will be capable of robust manufacturing of tilmanocept API.

Additionally, the potency assay, which was found inadequate during a pre-approval inspection of (b) (4), was modified and moved to (b) (4) late in the first review cycle. The adequacy of the establishment with respect to the amendment will be fully evaluated during the re-submission review cycle.

2. The CMOs have developed corrective action plans including implementation timing based upon the 483 observations.
 - 2a. Does FDA agree that these plans fully address the observations?

2b. Does the FDA agree with the completion timing for the corrective action plans?

2a+2b FDA response: As stated during the September 18 t-con, your CMOs' responses and corrective action plans to address significant deficiencies generally appear adequate. It should be noted that (b) (4) bioburden testing is expected to be performed (b) (4). For significant deficiencies, the corrective actions must be implemented prior to an approval recommendation. Re-inspection(s) may be needed to verify the implementation of the actions and make final determination(s) on the adequacy of the corrections.

3. We believe all other establishments in the NDA are satisfactory and no other actions are required at this time.

3a. Does FDA agree?

FDA response: At this time, all other manufacturing facilities appear acceptable to support an approval recommendation for NDA 202-207. However, the CGMP compliance of a facility can change independent of the application review process. It remains the sponsor's responsibility to ensure the selection and use of appropriate contract facilities. The compliance status of each facility named in the application may be re-evaluated upon re-submission.

4. Upon resubmission to address the CRL what will be the timing of the FDA review?

FDA response: This is a review issue. Upon receipt of the resubmission, the review team will determine whether it is a class I submission (2 month clock) or a class II submission (6 month clock). You will be notified once the determination has been made.

5. (b) (4)

(b) (4) was inspected by FDA (b) (4) District Office between (b) (4) and Navidea understands that (b) (4) may be re-inspected in October. Assuming satisfactory results, will this re-inspection serve to fully address and remove the (b) (4) withhold status and close the CRL issues related to the (b) (4) facility?

FDA response: The inspection plan is to focus solely on Tilmanocept and supporting GMP systems. An adequate inspection outcome would satisfy (b) (4) District Office for an approval recommendation of Tilmanocept API to CDER Office of Compliance. It is important to note that this is not planned to be a full GMP inspection.

6. (b) (4)

(b) (4) was inspected by FDA (b) (4) District Office between (b) (4) and are not aware of any re-inspection dates. Is a re-inspection of (b) (4) required to for the CRL resubmission?

FDA response: A re-inspection of either (b) (4) is not required prior to the CRL re-submission. You may re-submit your application when your contract manufacturers have adequately addressed the significant deficiencies, including implementation of corrective actions, and are ready for re-inspection. The decision to perform an additional inspection will be made during the re-submission review cycle.

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/s/

ALBERTA E DAVIS WARREN
10/04/2012



NDA 202207

MEETING REQUEST GRANTED

Navidea Biopharmaceuticals, Inc.
Attention: Rodger Brown
Vice President, Regulatory Affairs and Quality Assurance
425 Metro Place North
Suite 450
Dublin, OH 43017

Dear Mr. Brown:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lymphoseek®.

We also refer to your September 13, 2012 correspondence requesting a meeting to discuss the issues in the complete response letter pertaining to cGMP status at the two contract manufacturing organizations. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The meeting is scheduled as follows:

Date: October 9, 2012
Time: 4:00 pm – 5:00 pm
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

CDER participants:

Charles Ganley, M.D., Director, ODEIV
Shaw Chen, M.D., Ph.D., Deputy Director, ODEIV
Dwayne Rieves, M.D., Director, DMIP
Louis Marzella, M.D., Deputy Director, DMIP
Eric Duffy, Ph.D., Director, DNQAIII,
Ali Al-Hakim, Ph.D., Branch Chief, Branch VII, DNQAIII,
Eldon Leutinger, Ph.D., CMC Team Leader, DNQAIII
Ravindra Kasliwal, Ph.D., CMC Reviewer, Branch VII, DNQAIII
LCDR Tara Goen, Division Director (acting), OC, OMPQ, DGMPA
Derek Smith, Ph.D., Chemist, OC, OMPQ, DGMPA
(b) (4)

(b) (4)

Alex Gorovets, M.D., Clinical Team Leader, DMIP
Brenda Ye, M.D., Medical Officer, DMIP
Olayinka Dina, DVM, Ph.D., Pharmacology and Toxicology Reviewer, DMIP
Adebayo Lanionu, Ph.D., Supervisory Pharmacologist, DMIP
John Metcalfe, Ph.D., Microbiology Reviewer, OPS
Gene Williams, Ph.D., Clinical Pharmacology Team Leader, DCPV
Christy John, Ph.D., Clinical Pharmacology Reviewer, DCPV
Jyoti Zalkikar, Ph.D., Statistical Reviewer Team Leader, DBV
Satish Misra, Ph.D., Statistical Reviewer, DBV
Anthony Mucci, Ph.D., Statistical Reviewer, DBV
Alberta Davis-Warren, Regulatory Health Project Manager, DMIP

Please e-mail me any updates to your attendees at Alberta.Davis-Warren@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

A few days before the meeting, you may receive an email with a barcode generated by FDA's Lobbyguard system. If you receive this email, bring it with you to expedite your group's admission to the building. Ensure that the barcode is printed at 100% resolution to avoid potential barcode reading errors.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Alberta Davis-Warren, 301-796-3908.

Submit background information for the meeting (three paper copies or one electronic copy to the application and 25 desk copies to me) at least two weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by September 26, 2012, we may cancel or reschedule the meeting.

Submit the 25 desk copies to the following address:

Alberta Davis-Warren
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 2358
10903 New Hampshire Avenue
Silver Spring, Maryland
*Use zip code **20903** if shipping via United States Postal Service (USPS).*
*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

If you have any questions, call me at (301) 796-3908

Sincerely,

{See appended electronic signature page}

Alberta Davis-Warren, B.S.
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

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/s/

ALBERTA E DAVIS WARREN
09/19/2012

MEMORANDUM OF MEETING

DATE: September 18, 2012

APPLICATION NUMBER: NDA 202207 Lymphoseek

BETWEEN: **Navidea Biopharmaceuticals, Inc.:**

Mark Pykett, V.M.D., Ph.D., Navidea President and Chief Executive Officer
Brent Lawson, Senior Vice President and Chief Financial Officer, Treasurer and Secretary

Thomas Tulip, Ph.D., Navidea EVP & Chief Business Officer

William Regan, Regulatory consultant

Rodger Brown, V.P., Regulatory Affairs and Quality Assurance

AND

FDA

Eric Duffy, Ph.D., Director, DNQAIII,

Derek Smith, Ph.D., Chemist, OC, OMPQ, DGMPA

Dwaine Rieves, M.D., Director, DMIP

Alberta Davis-Warren, Regulatory Health Project Manager, DMIP

SUBJECT: Manufacturing Facility Deficiencies

HISTORY: On September 10, 2012 Navidea Biopharmaceuticals received a Complete Response letter for their Lymphoseek new drug application. In response to the CR letter, Navidea requested a type A meeting to discuss issues in the complete response letter pertaining to cGMP status at the two contract manufacturing organizations. The meeting request was granted and the meeting is scheduled for October 9, 2012. Navidea was notified of the proposed date and wanted the meeting sooner than October 9th. Since the meeting date can not be changed to an earlier date, Navidea requested a brief phone call with Dr. Duffy to discuss the manufacturing issues in order to prepare for the October 9, 2012 meeting.

TODAY'S Meeting:

In today's meeting, the following items were briefly discussed:

- FDA noted that the inspectional issues observed during pre-approval inspection of the (b) (4) manufacturing facilities appear to be nearing resolution since the remediation plans appear acceptable and the main outstanding concerns relate to implementation of the plans.
- FDA noted that definitive feedback with respect to the acceptability of the manufacturing remediation plans will involve the respective District Offices and the contract

- manufacturing facilities. As such, the October meeting is the best forum for discussion of the details of the outstanding issues, remediation plans and timelines, and the timing any follow-up inspections that may be needed.
- FDA offered to provide comments upon the “poster-type” presentation the company is developing to summarize the Dosage and Administration aspects from the labeling. The company noted that they are developing (b) (4) to assist nuclear pharmacists and the company will share this draft with the FDA in the future.
- FDA closed the conversation by reiterating the role of the full facility/manufacturing review team as has already been planned for the October meeting; more definitive information will be provided to the company at this meeting.

Dwaine Rieves, M.D.
Director, DMIP

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/s/

ALBERTA E DAVIS WARREN
10/19/2012

RAFEL D RIEVES
10/19/2012

Davis-Warren, Alberta E

From: Davis-Warren, Alberta E
Sent: Tuesday, September 11, 2012 6:03 PM
To: 'Brown, Rodger'
Cc: regulatoryaffairs
Subject: RE: Telecon Information

Dear Mr. Brown,

The Letter of Authorization (LOA) documents for [REDACTED] (b) (4) [REDACTED] are acceptable and we will discuss the manufacturing deficiencies with Navidea Biopharmaceuticals. Please submit the LOAs as an amendment to the NDA and submit an official meeting request. For both manufacturing sites, the discussion should include all parties (Navidea, the manufacturing site, and the Agency).

Please contact me if you have any questions.

Thank you,

Alberta

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
301-796-3908 office
301-796-9849 fax
Alberta.Davis-Warren@fda.hhs.gov

From: Brown, Rodger [mailto:rbrown@navidea.com]
Sent: Tuesday, September 11, 2012 9:51 AM
To: Davis-Warren, Alberta E
Cc: regulatoryaffairs
Subject: Telecon Information

Dear Ms. Davis Warren,

As a follow-up to the discussions between Dr. Pykett and the FDA review team yesterday, please find enclosed copies of letters of authorization between Navidea and our Suppliers, that were identified in the Complete Response Letter Dated 10 SEP 2012.

As Dr. Eric Duffy commented, Dr. Pykett did send these copies last evening directly to Dr. Eric Duffy.

Best regards,
Rodger

Rodger A. Brown | Vice President, Regulatory Affairs and Quality Assurance
Navidea Biopharmaceuticals
425 Metro Place North, Suite 450 | Dublin, OH 43017
phone 614.793.7500 x142 | fax 614.793.7520

regulatoryaffairs@navidea.com
rbrown@navidea.com
www.navidea.com

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/s/

ALBERTA E DAVIS WARREN
09/12/2012

MEMORANDUM OF MEETING

DATE: September 10, 2012

APPLICATION NUMBER: NDA 202207 Lymphoseek

BETWEEN: **Navidea Biopharmaceuticals, Inc.:**
Mark Pykett, V.M.D., Ph.D., Navidea President and Chief Executive Officer

AND

FDA

Charles Ganley, M.D., Director, ODEIV
Eric Duffy, Ph.D., Director, DNQAIII,
Dwayne Rieves, M.D., Director, DMIP
Louis Marzella, M.D., Ph.D., Deputy Director, DMIP
Alex Gorovets, M.D., Clinical Team Leader, DMIP
Alberta Davis-Warren, Regulatory Health Project Manager

SUBJECT: Manufacturing Facility Deficiencies

HISTORY: On September 10, 2012 Navidea Biopharmaceuticals received a Complete Response letter for the Lymphoseek new drug application. In response to the CR letter, Dr Pykett from Navidea Biopharmaceuticals requested a brief phone call with Dr. Rieves to discuss the CR letter. We informed Dr. Pykett that the phone call is granted and that other members from FDA will participate to provide input in the meeting.

TODAY'S Meeting:

The meeting started with the sponsor inquiring about the specific deficiencies from the two manufacturing facilities [REDACTED] (b) (4) FDA stated that they can not discuss the specific issues without authorization from the two manufacturing facilities. Dr. Pykett thought the issues were resolved with the manufacturing facilities. FDA replied that reviewing an application during the review cycle is an ongoing process. The decision was made last week by the Office of compliance and they determined that the two sites were unacceptable for approval.

Dr. Pykett asked if the resubmission will be reviewed under a two month clock or a six month clock. FDA replied it will probably be reviewed under a six month clock with the possibility of the action occurring prior to the PDUFA date. FDA advised Dr. Pykett to submit letters of authorization from the manufacturing facilities granting permission to the Agency to disclose confidential information regarding their sites to Navidea.

Alberta Davis-Warren
Regulatory Health Project Manager, DMIP

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/s/

ALBERTA E DAVIS WARREN
10/19/2012

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 202207 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Lymphoseek Established/Proper Name: Tilmanocept Dosage Form: Powder for Injection		Applicant: Navidea Biopharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Alberta Davis-Warren		Division: Division of Medical Imaging Products
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A 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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>9-10-12</u> • Previous actions (<i>specify type and date for each action taken</i>) 		<input type="checkbox"/> AP <input type="checkbox"/> TA <input checked="" type="checkbox"/> CR <input checked="" type="checkbox"/> None

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics ³</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): Radioactive Diagnostic Agent</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)</p> <p>Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Communication Plan <input type="checkbox"/> Submitted in response to a Pediatric Written Request <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required</p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> • Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> • Press Office notified of action (by OEP) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> • Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLA: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist ⁴	X
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) 9-10-12
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	X
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	X
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	X
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	8-7-12 & 11-16-11
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 10-21-11 <input checked="" type="checkbox"/> DMEPA 6-22-12 <input type="checkbox"/> DMPP/PLT (DRISK) <input checked="" type="checkbox"/> ODPD (DDMAC) 4-3-12 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews PMHS 4-10-12
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	RPM filing review 10-12-11
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte 	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>4-11-12</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>) 	<input checked="" type="checkbox"/> Verified, statement is acceptable

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications (letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)	X
❖ Internal memoranda, telecons, etc.	X
❖ Minutes of Meetings	
• Regulatory Briefing (indicate date of mtg)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (indicate date of mtg)	<input type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (indicate date of mtg)	<input checked="" type="checkbox"/> [REDACTED] 10-4-10
• EOP2 meeting (indicate date of mtg)	<input checked="" type="checkbox"/> [REDACTED] 10-24-07
• Other milestone meetings (e.g., EOP2a, CMC pilots) (indicate dates of mtgs)	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (do not include transcript)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (indicate date for each review)	<input checked="" type="checkbox"/> [REDACTED] 9-7-12
Division Director Summary Review (indicate date for each review)	<input checked="" type="checkbox"/> [REDACTED] 8-25-12
Cross-Discipline Team Leader Review (indicate date for each review)	<input checked="" type="checkbox"/> [REDACTED] 7-30-12
PMR/PMC Development Templates (indicate total number)	<input checked="" type="checkbox"/> None
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (indicate date for each review)	See CDTL Review dated 7-30-12
• Clinical review(s) (indicate date for each review)	7-16-12 & 8-27-12
• Social scientist review(s) (if OTC drug) (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (indicate date of review/memo)	See Clinical Review dated 8-27-12
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review)	<input checked="" type="checkbox"/> [REDACTED] DOP2 3-15-12 PMHS 4-3-12 & 12-21-11
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement (indicate date(s) of submission(s))	
• REMS Memo(s) and letter(s) (indicate date(s))	
• Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review)	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators)	<input checked="" type="checkbox"/> [REDACTED] 2-9-12

⁶ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> [REDACTED] Co-signed primary review dated 7-25-12
Statistical Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> [REDACTED] 7-25-12
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> [REDACTED] Co-signed primary review dated 7-12-12
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> [REDACTED] 7-12-12
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of DSI letters)</i>	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> [REDACTED] 7-26-12
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> [REDACTED] Co-signed primary review dated 6-27-12
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> [REDACTED] 6-27-12
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary <i>(include copies of DSI letters)</i>	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> [REDACTED] 9-5-12
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> [REDACTED] 7-19-12, 7-20-12 & 8-27-12
❖ Microbiology Reviews	<input checked="" type="checkbox"/> [REDACTED] 4-9-12
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None

❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)		See CMC review dated 7-19-12
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)		
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)		
❖ Facilities Review/Inspection		
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷</i>)		Date completed: 8-30-12 <input type="checkbox"/> Acceptable <input checked="" type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)		<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input checked="" type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
- (3) **Or** 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) **And** 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.
- (3) **And** 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) **Or** 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.
- (3) **Or** 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 ODE's ADRA.

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
09/10/2012

Davis-Warren, Alberta E

From: Davis-Warren, Alberta E
Sent: Thursday, September 06, 2012 11:08 AM
To: 'Brown, Rodger'
Cc: regulatoryaffairs
Subject: RE: Response and Update to FDA Email 29AUG2012 - CMC Status

Dear Mr. Brown,

We appreciate your efforts to work with your contract manufacturers, including your insights into the remaining deficiencies at these sites. Please be aware that we are requesting no additional information at the present time and cannot review any subsequent submissions to your NDA.

Regards,
Alberta

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
301-796-3908 office
301-796-9849 fax
Alberta.Davis-Warren@fda.hhs.gov

FDA does not ensure the security of email communications. If you desire to communicate by secure email, please establish a secure email channel by contacting SecureEmail@fda.hhs.gov.

From: Brown, Rodger [mailto:rbrown@navidea.com]
Sent: Wednesday, September 05, 2012 3:09 PM
To: Davis-Warren, Alberta E
Cc: regulatoryaffairs
Subject: Response and Update to FDA Email 29AUG2012 - CMC Status

Dear Ms. Davis-Warren:

Thank you for providing FDA's response to our question regarding the status of CMC activities regarding the Lymphoseek NDA 202207.

From FDA's email on August 29, 2012:

“The final recommendation on the acceptability of your contract manufacturing facilities will be made by the Office of Compliance. The inspectional findings are currently under review. Your contract manufacturers should continue to update the district offices on the progress of corrective actions following the most recent pre-approval inspections. You may wish to contact your contract manufacturers to obtain insight into their most recent corrective action plans.”

As required by Navidea's quality management system and the formal Quality Agreements with each CMO, Navidea is fully engaged with these Suppliers and all facilities involved in the NDA and preparations for commercial release. We conduct frequent telephone conferences and onsite meetings

with these Suppliers to fully address the inspectional observations. Additionally, we are obtaining Letters of Authorization from each of these Suppliers so that if the need arises we can discuss any issues regarding the CMOs directly with the Office of Compliance.

We continue to be an integral part of all remediation activities with our Suppliers and the FDA. We collaborated with the CMOs on the development of corrective action plans, timelines, and District Office communications. In addition Navidea provided additional resources (equipment and manpower) to these facilities in order to address critical elements of the corrective action plans including the revised and validated analytical potency method for the drug product.

These corrective action plans were communicated to the District offices through our Suppliers and appear satisfactory to address the inspectional observations, and to move the compliance status of these facilities forward in support of the Lymphoseek September 10, 2012 PDUFA date. Navidea and the Suppliers have not received communications from FDA that would cause us to believe the proposed corrective action plans are not adequate or do not support the PDUFA date.

Finally, we remain fully committed to working directly with each of our Suppliers and FDA to facilitate and maintain compliance with cGMPs as mandated by Navidea's quality management system and the individual quality agreements with these Suppliers to ensure ongoing and continuous adherence to high standards of safety, quality and compliance.

Please contact me directly regarding this communication.

Best regards,
Rodger

Rodger A. Brown | Vice President, Regulatory Affairs and Quality Assurance

Navidea Biopharmaceuticals

425 Metro Place North, Suite 450 | Dublin, OH 43017

phone 614.793.7500 x142 | fax 614.793.7520

regulatoryaffairs@navidea.com

rbrown@navidea.com

www.navidea.com

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/s/

ALBERTA E DAVIS WARREN
09/06/2012

Davis-Warren, Alberta E

From: Davis-Warren, Alberta E
Sent: Wednesday, September 05, 2012 4:04 PM
To: Brown, Rodger
Cc: regulatoryaffairs
Subject: NDA 202207 Lymphoseek Label

Importance: High

Attachments: FDAtoNavidea9-5-12TrackChangesdraft-labeling-text.doc; FDAtoNavidea9-5-12CLEANdraft-labeling-text.doc

Dear Mr. Brown,

We are supplying a proposed revision of the prescribing information. We encourage you to examine this labeling and to supply an amendment to your NDA as soon as possible (our review of labeling alterations will conclude on Friday morning/September 7). Justify any alterations to the text. We have tried to detect typographical errors but may have missed some; we appreciate your correction of any typographical errors. Regarding the revision:

- 1) The highlights section (not the full prescribing information) must contain the FDA recognized pharmacological class of the drug (radioactive diagnostic agent), so our revision maintains the recognized pharmacological class; nevertheless, we tried to address your desire to include the "lymphatic mapping" role of the drug within the indication statement.
- 2) Our review team manufacturing experts could not concur with your proposed additional sentence in the Description section (b) (4) and recommended retention of the original text.



FDAtoNavidea9-5-1
2TrackChanges...



FDAtoNavidea9-5-1
2CLEANdraft-I...

Please contact me if you have any questions.

Thank you,
Alberta

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
301-796-3908 office
301-796-9849 fax
Alberta.Davis-Warren@fda.hhs.gov

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/s/

ALBERTA E DAVIS WARREN
09/06/2012

Davis-Warren, Alberta E

From: Davis-Warren, Alberta E
Sent: Wednesday, August 29, 2012 12:00 PM
To: 'Brown, Rodger'
Cc: regulatoryaffairs
Subject: RE: Navidea Question

Dear Mr. Brown,

Please see the response to your question:

Navidea question: Does the Agency find this plan acceptable?

The final recommendation on the acceptability of your contract manufacturing facilities will be made by the Office of Compliance. The inspectional findings are currently under review. Your contract manufacturers should continue to update the district offices on the progress of corrective actions following the most recent pre-approval inspections. You may wish to contact your contract manufacturers to obtain insight into their most recent corrective action plans.

Thank you,
Alberta

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
301-796-3908 office
301-796-9849 fax
Alberta.Davis-Warren@fda.hhs.gov

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From: Brown, Rodger [mailto:rbrown@navidea.com]
Sent: Friday, August 10, 2012 11:38 PM
To: Davis-Warren, Alberta E
Cc: regulatoryaffairs
Subject: Navidea Question

Dear Ms. Davis-Warren:

Thank you for responding to our email and voicemail yesterday, and following up with me today.

This email is intended to clarify Navidea's question stemming from our communication with you on Wednesday, August 8, 2012.

Navidea understands from FDA guidance that it is required to have the drug substance manufacturing validation protocol in place at the time of approval.

Navidea further understands from (b) (4) has communicated to the FDA (b) (4) District Office that the validation protocol will be in place by August 20, 2012, in advance of the PDUFA date for Lymphoseek NDA 202207 on September 10, 2012. Please see the email below from (b) (4) to the (b) (4) District Office.

Navidea understands that the FDA (b) (4) District Office has requested completion of one manufacturing validation lot and re-inspection of the (b) (4) facility upon completion.

Navidea understands from (b) (4) has committed to the (b) (4) District Office to complete the one manufacturing validation and request a re-inspection by the (b) (4) District Office (b) (4).

(b) (4) has also asked the District Office to update (b) (4) on the status of the CDER Withhold Recommendation. Please see the email below from (b) (4) to the (b) (4) District Office.

Navidea question: Does the Agency find this plan acceptable?

Best regards,
Rodger

Rodger A. Brown | Vice President, Regulatory Affairs and Quality Assurance

Navidea Biopharmaceuticals

425 Metro Place North, Suite 450 | Dublin, OH 43017

phone 614.793.7500 x142 | fax 614.793.7520

regulatoryaffairs@navidea.com

rbrown@navidea.com

www.navidea.com

From: (b) (4)
Sent: Friday, August 10, 2012 4:00 PM
To: (b) (4)
Subject: FW: Tilmanocept Follow-Up

Hello (b) (4)

I hope you are getting some of the nice weather we are seeing here in (b) (4). I appreciate our discussion this morning, and confirm as you have consistently stated that for product approval we need to have an approved Process Validation Protocol and NDA product approval is not subject to validation batch completion.

As in my previous email dated 8/9/2012, we agree and understand that a follow-up inspection should take place after the completion of Validation Batch One. We anticipate the completion of our Process Validation Protocol on or before August 20th, 2012. Upon completion of the protocol we will begin the final API manufacturing of batch one. Batch one completion is targeted (b) (4).

Within the next 2 weeks I will request the follow-up audit through (b) (4) to be conducted on or around (b) (4).

The question I have now, which I believe is the question Navidea is also asking through CDER. Knowing all of these timelines, does this affect the status of the withhold recommendation?

Have a great weekend,

(b) (4)

(b) (4)

President and CEO

Phone: (b) (4)

(b) (4)

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/s/

ALBERTA E DAVIS WARREN
09/06/2012

Davis-Warren, Alberta E

From: Davis-Warren, Alberta E
Sent: Friday, August 24, 2012 3:09 PM
To: 'Brown, Rodger'
Cc: regulatoryaffairs
Subject: NDA 202207 Lymphoseek labeling

Importance: High

Attachments: 8-24-12FDAtoLymphoseek redline-draft-labeling-text.doc; Comments for Tilmanocept Powder vial label.doc

Dear Mr. Brown,

Attached are FDA's revisions to the Lymphoseek package insert and FDA's comments regarding the carton and container labeling.



8-24-12FDAtoLymphoseek redline...



Comments for Tilmanocept Powde..

Please review the information and please provide an amendment with the revised labeling as soon as possible.

Please contact me if you have any questions.

Thank you,
Alberta

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
301-796-3908 office
301-796-9849 fax
Alberta.Davis-Warren@fda.hhs.gov

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/s/

ALBERTA E DAVIS WARREN
08/24/2012

MEMORANDUM OF MEETING

DATE: August 16, 2012

APPLICATION NUMBER: NDA 202207 Lymphoseek

BETWEEN: **Navidea Biopharmaceuticals, Inc.:**
Mark Pykett, President/CEO
Thomas Tulip, EVP and Chief Business Officer
Fred Cope, Sr. VP, Clinical Research and Pharmaceutical Development
Ann Maloney, Dir. Pharmaceutical Development and Compliance (CMC)
William Regan, Regulatory Consultant
George Mills, Regulatory Consultant
Wendy Metz, Associate Director, Clinical Research
Dave Pendleton, Mktg. Consultant
Rodger Brown, VP, RA/QA

AND

Division of Medical Imaging Products, HFD-160
Dwayne Rieves, M.D., Director, DMIP
Louis Marzella, M.D., Ph.D., Deputy Director, DMIP
Eldon Leutzinger, Ph.D., CMC Team Leader, DNQAIII
Alex Gorovets, M.D., Clinical Team Leader, DMIP
Lucie Yang, M.D., Ph.D., Clinical Team Leader, DMIP
John Metcalfe, Ph.D., Microbiology Reviewer, OPS
Olayinka Dina, DVM, Ph.D., Pharmacology/Toxicology Reviewer, DMIP
Gene Williams, Ph.D., Clinical Pharmacology Team Leader, DCPV
Satish Misra, Ph.D., Statistical Reviewer, DBV
Jyoti Zalkikar, Ph.D., Statistical Team Leader, DBV
Shaw Chen, M.D., Deputy Director, ODEIV
Alberta Davis-Warren, Regulatory Health Project Manager, DMIP

SUBJECT: Quick Component Guide for Lymphoseek Labeling

HISTORY: On July 11, 2012 the Division started labeling negotiations with Navidea Biopharmaceuticals by providing the Lymphoseek package insert with comments, and comments regarding the carton and container labeling to the sponsor to review. On July 18, 2012 Navidea sent to the Division their revisions to the labels along with additional comments. The sponsor made several changes to the package insert. The Division is very concerned with the extent of the changes made, especially those in the dosage and administration (D&A) section of the label. The section that explains the reconstitution of the product is very complicated. The Division has decided that based on the information in the D&A section, a quick guide component that contains illustrations is needed for nuclear pharmacists. The purpose for the teleconference is to discuss with the sponsor adding a quick guide component to Lymphoseek.

TODAY'S Meeting:

During the teleconference, FDA conveyed the following information to the sponsor:

1—We are currently working on a labeling proposal. We hope to have a revised labeling proposal to you by the end of next week. This will likely be the last opportunity for the company to vet the labeling proposal before the action due date.

2—The main reason we are calling is to inform the company that we are requesting a poster-type quick guide document to be potentially included as a component of labeling or as promotional material; this poster-type document would clearly and simply illustrate the reconstitution procedures (as described in the dosage and administration section of labeling). We are working to clarify whether this should be incorporated into labeling or regarded as marketing material. We will provide this advice to the company.

3—The review team cannot support the

(b) (4)

The sponsor inquired as to when they receive the proposed labeling. The Division will try to send the label to the sponsor by the end of next week; however, due to the complexity of the label and that the sponsor made so many revisions to the label, the Division could not guarantee it. The Division also stated to the sponsor that they deleted standard regulatory language in the label that must be placed back in the label. The Division mentioned that the carton and container labeling needed only a few revisions.

The company understood the Division's comments and the sponsor preferred if possible to create marketing material instead of incorporating a guide in the label.

Alberta Davis-Warren, BS
Regulatory Health Project Manager

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/s/

ALBERTA E DAVIS WARREN
08/20/2012

Davis-Warren, Alberta E

From: Davis-Warren, Alberta E
Sent: Friday, July 27, 2012 11:36 AM
To: 'Brown, Rodger'
Cc: regulatoryaffairs
Subject: NDA 202207 Lymphoseek - 7-26-12 voice mail message, FDA attendees 7-20-12 meeting

Dear Mr. Brown,

In regards to your voice mail message I received yesterday, CMC had an action item from the 7-20-12 meeting. The action item is CMC will provide feedback to question 2F in the meeting package. Here are the comments from CMC:

Question 2f re setting a spec (b) (4) has been reconsidered - Navidea need not pursue this.

Also here is the list of FDA attendees from the 7-20-12 CMC meeting:

Dwaine Rieves, M.D., Director, DMIP
Eric Duffy, Ph.D., Director, DNQAIII
Ali Al-Hakim, Ph.D., Branch Chief, Branch VII, DNQAIII
Eldon Leutzinger, Ph.D., CMC Team Leader, DNQAIII
Ravindra Kasliwal, Ph.D., CMC Reviewer, Branch VII, DNQAIII
Alex Gorovets, M.D., Clinical Team Leader, DMIP (called in)
Lucie Yang, M.D., Ph.D., Clinical Team Leader, DMIP
Brenda Ye, M.D., Medical Officer, DMIP
Olayinka Dina, DVM, Ph.D., Pharmacology and Toxicology Reviewer, DMIP (called in)
John Metcalfe, Ph.D., Microbiology Reviewer, OPS
Ira Krefting, M.D., Safety Deputy Director, DMIP
LCDR Tara Gooen, Division Director (acting), Office of Compliance,
Office of Manufacturing and Product Quality, Division of Good Manufacturing
Practice Assessment
Charles Ganley, M.D., Director, ODEIV
Alberta Davis-Warren, Regulatory Health Project Manager, DMIP

Please contact me if you have any questions.

Thank you,

Alberta

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
301-796-3908 office
301-796-9849 fax
Alberta.Davis-Warren@fda.hhs.gov

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/s/

ALBERTA E DAVIS WARREN
07/27/2012



NDA 202207

MEETING MINUTES

Navidea Biopharmaceuticals, Inc.
Attention: Rodger A. Brown
Vice President, Regulatory Affairs and Quality Assurance
425 Metro Place North
Suite 450
Dublin, Ohio 43017

Dear Mr. Brown:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lymphoseek.

We also refer to the meeting between representatives of your firm and the FDA on July 20, 2012. The purpose of the meeting was to discuss the new analytical potency method for Lymphoseek.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3908.

Sincerely,

{See appended electronic signature page}

Alberta Davis-Warren, B.S.
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Guidance

Meeting Date and Time: July 20, 2012 2:00 pm – 3:00 pm
Meeting Location: White Oak Building 22 Conference Room 1415

Application Number: NDA 202207
Product Name: Lymphoseek
Indication: (b) (4) localization of tumor-draining lymph nodes in patients with breast cancer or melanoma.

Sponsor/Applicant Name: Navidea Biopharmaceuticals, Inc.

Meeting Chair: Eric Duffy, Ph.D.
Meeting Recorder: Alberta Davis-Warren, B.S.

FDA ATTENDEES

Dwaine Rieves, M.D., Director, DMIP
Eric Duffy, Ph.D., Director, DNQAIII,
Ali Al-Hakim, Ph.D., Branch Chief, Branch VII, DNQAIII,
Eldon Leutzinger, Ph.D., CMC Team Leader, DNQAIII
Ravindra Kasliwal, Ph.D., CMC Reviewer, Branch VII, DNQAIII
Alex Gorovets, M.D., Clinical Team Leader, DMIP (called in)
Lucie Yang, M.D., Ph.D., Clinical Team Leader
Brenda Ye, M.D., Medical Officer, DMIP
Olayinka Dina, DVM, Ph.D., Pharmacology and Toxicology Reviewer, DMIP (called in)
John Metcalfe, Ph.D., Microbiology Reviewer, OPS
Ira Krefting, M.D., Safety Deputy Director, DMIP
LCDR Tara Goen, Division Director (acting), OC, OMPQ, DGMPA
Charles Ganley, M.D., Director, ODEIV
Alberta Davis-Warren, Regulatory Health Project Manager, DMIP

SPONSOR ATTENDEES

Mark Pykett, V.M.D., Ph.D., President/CEO
Ann Maloney, Director, Drug Development and Compliance (b) (4)
Rodger Brown, Vice President, Regulatory Affairs and Quality Assurance
(called in)
George Mills . M.D.. Consultant. Drug Development – Clinical and Regulatory (b) (4)
William Regan, Regulatory Consultant

1. BACKGROUND

On August 10, 2011 Navidea Biopharmaceuticals submitted a new drug application (NDA) for the product Lymphoseek to the Division of Medical Imaging Products. Part of the review process for NDAs entail inspecting the drug products manufacturing facilities. During review and the inspection of one of the facilities involved in testing of Lymphoseek, it was found that the method of determining potency (assay) has problems and the assay is not acceptable in its current form. As a result, CMC sent an information request to Navidea asking them to provide an accurate potency assay. The purpose of this meeting is to discuss the new analytical potency method for Lymphoseek and other related issues.

2. DISCUSSION

After introductions of the meeting participants, the Applicant discussed their responses to FDA's comments in the meeting package.

Question 1.

(b) (4)

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5.0 ACTION ITEMS

- CMC review team will provide feedback to Question 2f during the week of July 23rd, 2012.
- During the meeting it was acknowledged that CMC needs more time to review the information Navidea provided for the meeting today. CMC will review Navidea's comments at a later time and if needed will add post-meeting feedback comments to the meeting minutes.
- FDA will send final labeling comments to Navidea in mid-August.

6.0 Post-Meeting Comments

Upon reconsideration of the Agency's request for Navidea to establish a method to quantitate (b) (4) in the product, FDA understands the technical obstacles that Navidea has presented, and therefore FDA has withdrawn the request.

7.0 ATTACHMENTS AND HANDOUTS

(b) (4) Method validation report for Lymphoseek

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/s/

ALBERTA E DAVIS WARREN
08/16/2012



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV
Division of Medical Imaging Products**

FACSIMILE TRANSMITTAL SHEET

DATE: July 19, 2012

To: Rodger A. Brown Vice President, Regulatory Affairs and Quality Assurance	From: Alberta E. Davis-Warren Regulatory Health Project Manager Alberta.Davis-Warren@fda.hhs.gov
Company: Navidea Biopharmaceuticals	Division of Medical Imaging Products
Email: rbrown@navidea.com	Fax number: 301-796-9849
Phone number: 614-793-7500 x142	Phone number: 301-796-3908
Subject: Preliminary responses for NDA 202207 Lymphoseek Type C Meeting	

Total no. of pages including cover: 5

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Dear Mr. Brown,

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for July 20, 2012, 2:00 pm - 3:00 pm, White Oak Bldg. 22, Room 1415 between Navidea Biopharmaceuticals and FDA. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any

modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting. Your question appears in *italics* below, followed by FDA's responses in **boldface**.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

**PRELIMINARY RESPONSES for July 20, 2012 Type C Meeting with
Navidea Biopharmaceuticals 2:00 PM – 3:00 PM
(NDA 202207, Lymphoseek)**

(b) (4)



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/s/

ALBERTA E DAVIS WARREN
07/19/2012

Davis-Warren, Alberta E

From: Davis-Warren, Alberta E
Sent: Wednesday, July 11, 2012 11:16 AM
To: 'Brown, Rodger'
Cc: regulatoryaffairs
Subject: NDA 202207 Lymphoseek labels

Importance: High

Attachments: LymphoseekLabelingCommentsfromFDA7-9-12.doc; LymphoseekPI7-9-12.doc

Dear Mr. Brown,

Attached are Lymphoseek labeling comments from the FDA and a clean version of the Lymphoseek package insert.



LymphoseekLabelin
gCommentsfrom...



LymphoseekPI7-9-1
2.doc (336 KB...

Please review both documents and please send the revised labeling by next Wednesday, July 18, 2012. Please contact me if you have any questions.

Thank you,
Alberta

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
301-796-3908 office
301-796-9849 fax
Alberta.Davis-Warren@fda.hhs.gov

Lymphoseek NDA 202207
Container Label and Carton Labeling Comments/See Attached CLEAN Version of
Package Insert
7/9/2012

General Comments

We are providing these preliminary comments in order for you to submit revised labeling (container labels and package insert) to your NDA as an amendment. Many changes must be made in your proposed labeling and the items described below and in the attached package insert must be addressed before we can further comment on the sufficiency of the labeling. The supplied labeling contained inconsistencies in text, incorrect description of kit contents and multiple other deficiencies. We are supplying you with a clean copy version for you to edit (a red line version is largely indecipherable because we had to change almost all aspects of the text). We remain unclear of whether or not your drug is for intradermal, subcutaneous as well as (b) (4) and we are also unsure of the dosage and administration directions. We have attempted to clarify these aspects within the package insert but we need you to further clarify the text (for example, is your drug only for subcutaneous or intradermal injection?). Please be aware that the manufacturing deficiencies are the subject of an upcoming meeting discussion and our provision of this draft labeling to you should not be interpreted as an indication that those issues have been resolved. Also, these are not our final comments upon your proposed labeling; submission of revised container labels and a package insert is necessary for us to understand important details of your labeling proposal.

Please note that we do not regard your clinical data as sufficient to support

(b) (4)

Within the kit, 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, expiration date/time, and radioactivity symbol.

Also, include the five "Radiolabeled Product" labels within the kit. If we understand correctly, the package insert refers to (b) (4) different types of labels

that are supplied within the kit (however, you supplied text for only (b) (4) of the labels).

Regarding your container labels:

A. Tilmanocept Powder Vial Container Label

1. Add a NDC number on the upper third portion of the principal display panel.
2. Delete the company logo, Navidea.
3. Revise the vial title from (b) (4) to read “Tilmanocept Powder for preparation of Lymphoseek (technetium Tc 99m tilmanocept) Injection.”
4. Revise the strength from “0.25 mg Tilmanocept per vial” to read “250 mcg per vial.”
5. Add the statements:

Administer only after radiolabeling with technetium Tc 99m
See insert for preparation and administration instructions
Single Use Vial - Discard Unused Portion
6. Delete the statements:

(b) (4)
7. Delete the current storage information and add the following storage information:

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.

B. Sterile Buffered Diluent Vial Container Label

1. Include a NDC number on the upper third portion of the principal display panel and the statement, Rx Only.
2. Revise the name to “DILUENT for Lymphoseek”. Additionally, use color scheme for the diluent vial labels that clearly distinguishes it from the Tilmanocept powder vials.
3. Add 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

4. Revise the current storage information 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.

The storage information should appear toward the bottom portion of the
principal display panel.

5. Add the lot and expiration date to the side panel.
6. 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.

C. Lymphoseek Carton Labeling

1. Relocate the list of kit contents from the side panel to the principal display
panel.
2. Revise the established name to “Kit for the preparation of (technetium Tc
99m tilmanocept) injection”, and place is below trademark Lymphoseek.
3. Revise the strength statement, “0.25 mg” to read “250 mcg.”
4. Decrease the prominence of the strength statement by decreasing the width
of the background.
5. Relocate the statement, Rx Only toward the bottom of the principal
display panel

6. Revise the current storage information 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.

7. Relocate the company logo/graphic from the principal display panel to the
rear panel.
8. Remove (b) (4) at the top of the rear panel.
These numbers do not provide useful information to nuclear pharmacists.

D. Radioassay Information Label

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 current storage information to read as follows:

Store at 25°C (77 °F) (USP controlled room temperature).

See the attached Word Document labeled, “LymphoseekPI7-9-12”

13 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ALBERTA E DAVIS WARREN
07/11/2012



NDA 202207

MEETING REQUEST GRANTED

Navidea Biopharmaceuticals, Inc.
Attention: Roger A. Brown
Vice President, Regulatory Affairs and Quality Assurance
425 Metro Place North
Suite 450
Dublin, OH 43017

Dear Mr. Brown:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lymphoseek.

We also refer to your June 5, 2012, correspondence requesting a meeting to discuss the analytical potency method for Lymphoseek. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting.

The meeting is scheduled as follows:

Date: July 20, 2012
Time: 2:00 pm -3:00 pm
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

CDER participants: Dwaine Rieves, M.D., Director, DMIP
Louis Marzella, M.D., Ph.D., Deputy Director, DMIP
Alex Gorovets, M.D., Clinical Team Leader, DMIP
Brenda Ye, M.D., Medical Officer, DMIP
Eric Duffy, Ph.D., Director, DNQAIII,
Ali Al-Hakim, Ph.D., Branch Chief, Branch VII, DNQAIII,
Eldon Leutzinger, Ph.D., CMC Team Leader, DNQAIII
Ravindra Kasliwal, Ph.D., CMC Reviewer, Branch VII, DNQAIII
Youbang Liu, Ph.D., Regulatory Health Project Manager, DNQAIII
Adebayo Lanionu, Ph.D., Supervisory Pharmacologist, DMIP
Olayinka Dina, DVM, Ph.D., Pharmacology/Toxicology Reviewer, DMIP
Gene Williams, Ph.D., Clinical Pharmacology Team Leader, DCP5
Christy John, Ph.D., Clinical Pharmacology Reviewer, DCP5
John Metcalfe, Ph.D., Microbiology Reviewer, OPS
Satish Misra, Ph.D., Statistical Reviewer, DBV

Anthony Mucci, Ph.D., Statistical Reviewer, DBV
Jyoti Zalkikar, Ph.D., Statistical Team Leader, DBV
Charles Ganley, M.D., Director, ODEIV
Shaw Chen, M.D., Deputy Director ODEIV
Alberta Davis-Warren, Regulatory Health Project Manager, DMIP

Please e-mail me any updates to your attendees at Alberta.Davis-Warren@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

A few days before the meeting, you may receive an email with a barcode generated by FDA's Lobbyguard system. If you receive this email, bring it with you to expedite your group's admission to the building. Ensure that the barcode is printed at 100% resolution to avoid potential barcode reading errors.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with the following number to request an escort to the conference room: Alberta Davis-Warren, 301-796-3908.

Submit background information for the meeting (three paper copies or one electronic copy to the application and 25 desk copies to me) at least three weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by **June 29, 2012** we may cancel or reschedule the meeting.

Submit the 25 desk copies to the following address:

Ms. Maribelle Ramos, Secretary
c/o Alberta Davis-Warren, RPM
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22 – Bay area 5243
10903 New Hampshire Avenue
Silver Spring, Maryland

Use zip code 20903 if shipping via United States Postal Service (USPS).

Use zip code 20993 if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).

If you have any questions, call me at (301) 796-3908.

Sincerely,

{See appended electronic signature page}

Alberta Davis-Warren, B.S.
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

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/s/

ALBERTA E DAVIS WARREN
06/21/2012



NDA 202207

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Navidea Biopharmaceuticals, Inc.
Attention: Rodger A. Brown
Vice President, Regulatory Affairs and Quality Assurance
425 Metro Place North
Suite 450
Dublin, Ohio 43017

Dear Mr. Brown:

Please refer to your August 10, 2011, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lymphoseek, (Tilmanocept) Powder for Injection and 0.25 mg vial.

On March 30, 2012, we received your March 30, 2012, solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is September 10, 2012.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by July 23, 2012.

If you have any questions, call me at (301) 796-3908.

Sincerely,

{See appended electronic signature page}

Alberta E. Davis-Warren, B.S.
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

ALBERTA E DAVIS WARREN
04/02/2012

MEMORANDUM OF MEETING

DATE: March 27, 2012

APPLICATION NUMBER: NDA 202207 Lymphoseek

BETWEEN: **Navidea Biopharmaceuticals**

Mark Pykett, President /CEO

Thomas Tulip, EVP & Chief Business Officer

Frederick Cope, Sr. V.P., Pharmaceutical Research and Clinical Development

Ann Maloney, Director, Drug Development and Compliance (CMC)

George Mills, Regulatory and Clinical Consultant

Dave Pendleton, acting V.P., Marketing & New Product Planning (Consultant)

Rodger Brown, V.P., Regulatory Affairs and Quality Assurance

William (Bill) Regan, Regulatory Project Manager for Lymphoseek - Europe

(b) (4)

AND

Division of Medical Imaging Products, HFD-160

Dwayne Rieves, MD, Director, DMIP (called in)

Louis Marzella, MD, PhD, Deputy Director, DMIP

Alex Gorovets, MD, Clinical Team Leader, DMIP

Brenda Ye, MD, Medical Officer, DMIP

Gene Williams, PhD, Clinical Pharmacology Team Leader, DCPV

Oluchi Elekwachi, PharmD, MPH, Regulatory Health Project Manager, PMHS

Alberta Davis-Warren, BS, Regulatory Health Project Manager, DMIP

SUBJECT: Proposed indication in the labeling in regards to addressing the Pediatric Plan

HISTORY: On August 10, 2011 Navidea Biopharmaceuticals submitted electronically a new drug application (NDA) for their product Lymphoseek to the Division of Medical Imaging Products. In the application the applicant requested a full waiver of pediatric studies since intraoperative lymphatic mapping (ILM) is limited to patients with breast cancer and melanoma. However the applicant's proposed indication (b) (4)

We placed a Pediatrics consult request to assist in providing input pertaining to the pediatric waiver request. Based on the applicant's proposed indication and feedback from Pediatrics, the Division denied the applicant's request for a full waiver of pediatric studies and Navidea had to submit a pediatric plan.

On February 2, 2012 Navidea submitted their pediatric plan for Lymphoseek to the Division. We consulted Pediatrics and Oncology to review the plan. Based on feedback from Oncology, the Division decided to request a teleconference with

Navidea to discuss changing their indication in the labeling to Breast cancer and Melanoma [REDACTED] (b) (4) and the most recent NDA review findings indicate that the applicant needs to modify their proposed indication.

TODAY'S Meeting: Dr. Rieves spoke to the company and informed the applicant that based on comments from Oncology and what has been reviewed thus far in the application, the Division recommends that Navidea Biopharmaceuticals change the indication to limit the applicable population to patients with breast cancer or melanoma. Dr. Rieves explained that [REDACTED] (b) (4)

[REDACTED] However if Navidea changed the indication specifically to breast cancer and melanoma the waiver for pediatric studies is a reasonable consideration and the division would recommend granting the waiver. Dr. Rieves asked the company to provide a response to our recommendation by noon Thursday, March 29, 2012. If Navidea agrees to change the indication, they should provide in their response a revised label with the new indication.

Action item:

Navidea Biopharmaceuticals will provide a response to the Division's recommendation by noon, Thursday, March 29, 2012. If the applicant agrees to the recommendation the applicant should provide a revised label with the new indications.

Alberta Davis-Warren, BS
Regulatory Health Project Manager

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/s/

ALBERTA E DAVIS WARREN
04/06/2012

FAX

**FOOD AND DRUG ADMINISTRATION
DIVISION OF MEDICAL IMAGING PRODUCTS**

5901-B Ammendale Road
Beltsville, Maryland 20705



To: Rodger A. Brown

From: Alberta Davis-Warren

FAX/EMAIL rbrown@navidea.com

FAX: 301-796-9849

Phone: 614-793-7500

Phone: 301-796-3908

Pages, including cover sheet: 3

Date: February 15, 2012

RE: Information Requests for NDA 202207

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the address above by mail. Thank you.

Dear Mr. Brown:

We make reference to your New Drug Application (NDA) for Lymphoseek, submitted on August 10, 2011 under section 505(b) of the Federal Food, Drug, and Cosmetic Act. We have the following CMC Information Requests:



(b) (4)

Please respond to these requests **as soon as possible**. Please submit an amendment to your application with your response to the requests using the official channels. To expedite the review process, please send me a courtesy copy through e-mail (Alberta.Davis-Warren@fda.hhs.gov) or FAX (301-796-9849) **as soon as possible**.

Thank you.

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
CDER, FDA

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/s/

ALBERTA E DAVIS WARREN
02/15/2012

FAX

**FOOD AND DRUG ADMINISTRATION
DIVISION OF MEDICAL IMAGING PRODUCTS**

5901-B Ammendale Road
Beltsville, Maryland 20705



To: Rodger A. Brown

From: Alberta Davis-Warren

FAX/EMAIL rbrown@navidea.com

FAX: 301-796-9849

Phone: 614-793-7500

Phone: 301-796-3908

Pages, including cover sheet: 4

Date: February 6, 2012

RE: Information Requests for NDA 202207

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the address above by mail. Thank you.

Dear Mr. Brown:

We make reference to your New Drug Application (NDA) for Lymphoseek, submitted on August 10, 2011 under section 505(b) of the Federal Food, Drug, and Cosmetic Act. During our review of the CMC section of your submission, we have the following Information Requests:





14. Provide data that show that the Lymphoseek will label with sodium pertechnetate solution obtained from each of the commercially available generator in the US.

Please respond to these requests by no later than **Friday, February 17, 2012 at 4:00 pm ET**. Please submit an amendment to your application with your response to the requests using the official channels. To expedite the review process, please send me a courtesy copy through e-mail (Alberta.Davis-Warren@fda.hhs.gov) or FAX (301-796-9849) no later than **Friday, February 17, 2012 at 4:00 pm ET**

Thank you.

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
CDER, FDA

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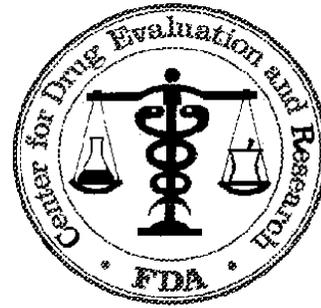
/s/

ALBERTA E DAVIS WARREN
02/06/2012

FAX

**FOOD AND DRUG ADMINISTRATION
DIVISION OF MEDICAL IMAGING PRODUCTS**

5901-B Ammendale Road
Beltsville, Maryland 20705



To: Rodger A. Brown **From:** Alberta Davis-Warren
FAX/EMAIL rbrown@navidea.com **FAX:** 301-796-9849
Phone: 614-793-7500 **Phone:** 301-796-3908
Pages, including cover sheet: 2 **Date:** January 26, 2012
RE: Information Request for NDA 202207

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the address above by mail. Thank you.

Dear Mr. Brown:

We make reference to your New Drug Application (NDA) for Lymphoseek, submitted on August 10, 2011 under section 505(b) of the Federal Food, Drug, and Cosmetic Act. During our review of your submission, we have the following Information Request:

Please submit a replica sample of Lymphoseek kit.

Please respond to the request by no later than **Thursday, February 2, 2012 at 3:00 pm ET**. Please send the replica kit to the following address:

Alberta Davis-Warren
FDA/CDER/DMIP
10903 New Hampshire Ave.
White Oak Bldg. 22 Room 2358
Silver Spring, MD 20993

Please contact me if you have any questions.

Thank you.

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
CDER, FDA

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/s/

ALBERTA E DAVIS WARREN
01/26/2012

Davis-Warren, Alberta E

From: Davis-Warren, Alberta E
Sent: Wednesday, January 18, 2012 2:17 PM
To: 'Brown, Rodger'
Cc: Jerew, Jean
Subject: RE: Pediatric Plan Waiver Denial Response

Dear Mr. Brown,

In response to your inquiry of January 16, 2012, we have the following comments:

- 1) Yes, submission of your pediatric plan by February 6, 2012 is reasonable.
- 2) In a citation to a potential “feasibility” study, we were envisioning a study that assesses the procedural success of your drug in a number of patients sufficient to provide useful descriptive information, even though the study is not powered for hypothesis testing. Feasibility studies are commonly used in the development of devices in order to refine technical details and to obtain pilot performance data in a limited number of subjects (sometimes as a prelude to larger sample size, phase 3 studies; see FDA web site of:
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm27>

In drug development, pediatric drug studies sometimes parallel the design of device feasibility studies, in terms of sample sizes and the descriptive nature of the endpoint analyses (for example, see the labeling for the anticoagulant, argatroban/Pfizer). The sample size in a feasibility study should be sufficient to obtain data that allow the extrapolation of safety and efficacy findings from adults to pediatric patients.

Please contact me if you have any questions. Also, please confirm receipt of this email.

Thank you,
Alberta

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
301-796-3908 office
301-796-9849 fax
Alberta.Davis-Warren@fda.hhs.gov

From: Brown, Rodger [mailto:rbrown@navidea.com]
Sent: Monday, January 16, 2012 4:40 PM
To: Davis-Warren, Alberta E
Cc: Jerew, Jean
Subject: Pediatric Plan Waiver Denial Response
Importance: High

Dear Ms. Davis -Warren,

We are in the final stages of preparing the complete response (pediatric plan) to the pediatric waiver denial letter of 23 DEC 2011. However, we need more guidance regarding FDA's definition of what is meant by "feasibility study". We assume this means information/data that supports the current standard of practice of imaging and detector probe use during the ILM procedures in pediatric trial subjects, as we described to the FDA review team during the 04 OCT 2011 Orientation Meeting for adult subjects. Please provide FDA's definition for a feasibility study.

Also, in addition to the question above, the waiver denial letter requires that we submit the pediatric plan by 23 JAN 2012. We have identified data sources that require an extension of 10 working days in order to fully complete this requirement. We respectfully request FDA consider an extension of the submission date to 06 FEB 2012 in order to fully address both items.

Best regards,
Rodger



Rodger A. Brown | Vice President, Regulatory Affairs and Quality Assurance

Navidea Biopharmaceuticals

425 Metro Place North, Suite 450 | Dublin, OH 43017-1367

phone 614.793.7500 x142 | direct 614.822.2342 | fax 614.822-2343

rbrown@navidea.com

www.navidea.com

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/s/

ALBERTA E DAVIS WARREN
01/18/2012



NDA 202207

**ACKNOWLEDGE CORPORATE
NAME/ADDRESS CHANGE**

Navidea Biopharmaceuticals, Inc.
Attention: Mr. Rodger A. Brown
Vice President, Regulatory Affairs and Quality Assurance
425 Metro Place North
Suite 450
Dublin, Ohio 43017

Dear Mr. Brown:

We acknowledge receipt on January 12, 2012 of your January 12, 2012 correspondence notifying the Food and Drug Administration (FDA) that the corporate name and/or address has been changed from

Neoprobe Corporation
425 Metro Place North
Suite 300
Dublin, Ohio 43017

to

Navidea Biopharmaceuticals, Inc.
425 Metro Place North
Suite 450
Dublin, Ohio 43017

for the following new drug application (NDA):

NDA 202207 for Lymphoseek[®], (Tilmanocept), powder for injection, 0.25 mg per vial

We have revised our records to reflect this change.

If your NDA references any Drug Master Files (DMF), we request that you notify your suppliers and contractors who have DMFs referenced by your NDA of the change so that they can submit a new letter of authorization (LOA) to their DMFs and send you a copy of the new LOAs. Please submit these copies of the LOAs to this NDA.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Medical Imaging Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me at (301) 796-3908.

Sincerely,

{See appended electronic signature page}

Alberta E. Davis-Warren, B.S.
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

ALBERTA E DAVIS WARREN
01/13/2012



NDA 202207

PREA WAIVER DENIED

Neoprobe Corporation
Attention: Mr. Rodger A. Brown
Vice President, Regulatory Affairs and Quality Assurance
425 Metro Place North
Suite 300
Dublin, Ohio 43017

Dear Mr. Brown:

Please refer to your submission dated August 10, 2011 requesting a waiver under 505B(a)(4) of the Federal Food, Drug, and Cosmetic Act for pediatric studies for Lymphoseek.

We have reviewed your submission and do not agree that a waiver of pediatric studies in patients under the age of 18 years is justified for Lymphoseek Kit for the Preparation of Technetium Tc 99m Tilmanocept for Injection. At this time, the proposed indication for this product is as follows: (b) (4)

[REDACTED]

We are denying this waiver for the following reasons:

- 1) The pediatric waiver request fails to provide justifications for such a waiver based on epidemiologic data for pediatric malignancies which could be likely to spread to the lymph nodes and for which Lymphoseek could be used intra-operatively for evaluation of tumor-draining lymph nodes.
- 2) You have indicated in your waiver request that, in fact, lymphatic mapping is performed in the pediatric population.
- 3) Although there might be insufficient number of patients to conduct an adequate and well-controlled pediatric efficacy and safety study, we believe there is adequate number of pediatric patients to conduct a pediatric pharmacokinetic, safety, and feasibility study.

Accordingly, a waiver for pediatric studies for this application is denied at this time. **We request that you submit your pediatric drug development plan by January 23, 2012.** Your pediatric drug development plan should address the same indication you are seeking for adults.

The Pediatric Research Equity Act allows for the extrapolation of pediatric effectiveness:

505B(a)(2)(B)(i) of the Food Drug & Cosmetic Act

IN GENERAL—If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, the Secretary may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies.

505B(a)(2)(B)(ii) of the Food Drug & Cosmetic Act

EXTRAPOLATION BETWEEN AGE - GROUPS—A study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group.

If you believe extrapolation of efficacy would be appropriate, provide a rationale for extrapolating efficacy from adult studies to the pediatric population.

In your proposed pediatric drug development plan, address the following:

1.

2.

3. Pharmacokinetics and safety of your product in children

4. Pediatric dosing (including time interval between drug administration and surgery) and pediatric dosing adjustments, if any

(b) (4)

We recommend that, in a planned pediatric study, you propose to enroll a representative number of patients (e.g. up to ten) from each of the age groups (0 to 2, 2 to 6, 6 to 12, and 12 to 18). If you plan to request a partial waiver applicable to a particular age group, submit a complete justification based on epidemiology, safety and other applicable considerations.

If you have questions, please call Alberta Davis-Warren, Regulatory Project Manager, at 301-796-3908.

Sincerely,

{See appended electronic signature page}

Rafel Dwaine Rieves, M.D.

Director

Division of Medical Imaging Products

Office of Drug Evaluation IV

Center for Drug Evaluation and Research

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/s/

RAFEL D RIEVES
12/23/2011

MEMORANDUM OF MEETING

DATE: December 20, 2011

APPLICATION NUMBER: NDA 202207 Lymphoseek

BETWEEN: **Neoprobe Corporation:**

Fred Cope; Sr. V.P. Pharmaceutical Research and Clinical Development
Dr. Michael Blue, Senior Medical Director
Rodger Brown; V.P., Regulatory Affairs and Quality Assurance
Mark Pykett; President and Chief Executive Officer
Richard McFerron; Associate Director, Regulatory Affairs Operations
Wendy Rich Metz; Associate Director, Medical Research Review and Development
George Mills; Regulatory and Clinical Consultant

(b) (4)

AND

Division of Medical Imaging Products, HFD-160

Dwaine Rieves, MD, Director
Alex Gorovets, MD, Clinical Team Leader
Brenda Ye, MD, Medical Officer
Satish Misra, PhD, Statistical reviewer, DBV
Anthony Mucci, PhD, Acting Statistical Team Leader, DBV
Jyoti Zalkikar, PhD, Statistical Team Leader, DBV
Jeanine Best, MSN, RN, PNP, Senior Clinical Analyst, Pediatric and Maternal Health Staff (PMHS)
Hari Sachs, MD, Clinical Team Leader, PMHS
Mildred Wright, RN, MSN, Regulatory Health Project Manager, PMHS
Alberta Davis-Warren, Regulatory Health Project Manager

SUBJECT: (b) (4) and Pediatric Waiver Request

HISTORY: On August 10, 2011 Neoprobe Corporation submitted electronically a new drug application (NDA) for their product Lymphoseek to the Division of Medical Imaging Products. On November 4, 2011 Neoprobe submitted revised labeling as an amendment to the NDA based on the 74 day filing issues identified letter sent by the Agency. Neoprobe revised their indication in the labeling to (b) (4)

On November 22, 2011 the Division sent the following information request to Neoprobe:

In the new Draft Labeling Text

(b) (4)

Please identify or provide the data supporting this claim.

Neoprobe contacted the Division for clarification of the information request. The Division decided to have a teleconference with Neoprobe to discuss the type of information they need to submit to support the claim of

(b) (4)

Also prior to the teleconference the Division decided to inform Neoprobe that their request for waiver of pediatric studies will be denied and that a pediatric plan will need to be submitted to the Agency.

TODAY'S Meeting:

Ms. Best from PMHS informed Neoprobe that their pediatric waiver request is going to be denied. During the discussion Neoprobe was told that lymphatic mapping is occurring more frequently in pediatric populations with soft tissue sarcomas, germ cell tumors, neuroblastoma, Wilms tumor and melanoma. Ms. Best also mentioned that they will receive a denial letter and that Neoprobe needs to submit a pediatric drug development plan that addresses at least the following:

1. 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;
2. A rationale for extrapolating efficacy from adult studies to the pediatric population based on dosimetry, if extrapolation of efficacy would be appropriate; and,
3. A complete justification for any partial waiver of pediatric studies.
4. A request for deferral and a plan that outlines the pediatric studies to be conducted.

After discussing the pediatric waiver request the Division explained to Neoprobe the information required to support the proposed indication in the label. Specifically the Division stated that Neoprobe need to provide an NDA amendment with textual information that explains the

(b) (4)

(b) (4). The Division may request the submission of datasets that support the summary analyses.

Neoprobe agreed to provide all of the requested information to the Division. The Division emphasized the importance in submitting the information in a timely manner since the application is running on a time clock. The denial letter will be sent in two weeks and we are asking for a response to the letter by the end of January 2012. The Pediatric plan will be reviewed by the Pediatric Review Committee.

Alberta Davis-Warren, BS
Regulatory Health Project Manager

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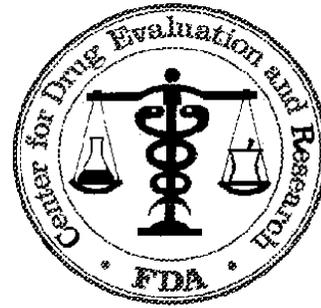
/s/

ALBERTA E DAVIS WARREN
12/22/2011

FAX

**FOOD AND DRUG ADMINISTRATION
DIVISION OF MEDICAL IMAGING PRODUCTS**

5901-B Ammendale Road
Beltsville, Maryland 20705



To: Rodger A. Brown **From:** Alberta Davis-Warren
FAX/EMAIL: RBROWN@neoprobe.com **FAX:** 301-796-9849
Phone: 614-793-7500 **Phone:** 301-796-3908
Pages, including cover sheet: 3 **Date:** December 13, 2011
RE: Information Requests for NDA 202207

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Dear Mr. Brown:

We make reference to your New Drug Application (NDA) for Lymphoseek, submitted on August 10, 2011 under section 505(b) of the Federal Food, Drug, and Cosmetic Act. During our review of the Microbiology section of your submission, we have the following Information Requests:

Comment #1.

Reference is made to USP<85> which states that the endotoxin limit for radiopharmaceutical products is 175/V, where V is the maximum recommended dose in mL. Reference is also made to Tables 1 and 2 of Module 3.2.P.5.1 of NDA 202207 which state that the limit for bacterial endotoxins is NMT (b) (4) for the lyophilized product and (b) (4) for the diluent.

It is unclear from your draft label what the number of vials is that will be required to formulate a maximum patient dose. If more than one product and diluent vial are required to prepare a dose, then the patient may potentially receive a higher amount of endotoxin than what is allowed in USP. In addition, the endotoxin limit stated in USP represents that which is allowable of the final drug product for patient administration, which is comprised of both the lyophilized product and its diluent.

- Provide the maximum number of vials that will be used to prepare a patient dose.
- Modify the bacterial endotoxins limit to be consistent with what is allowed in USP, taking into account the final product for administration (combination of lyophilized powder and diluent) as well as the number of product vials required to formulate a maximum patient dose.

Comment #2.

Reference is made to Table 2 of Module 3.2.P.3.3.9 which states that the (b) (4) bioburden acceptance criterion is (b) (4). For comparison, reference is made to USP<1231> which suggests that Water for Injection not contain > 10 CFU/100 mL. Your manufacturing process should not add a significant level of bioburden to the action level for WFI.

- Amend the application with a (b) (4) bioburden limit which is closer to the USP recommendation for Water for Injection.

Comment #3.

Reference is made to Module 3.2.P.3.5.3.4 which summarizes the bacterial retention validation studies for the (b) (4). The application states that “the (b) (4) validation file is available for inspection at (b) (4) and Neoprobe”, however this file was not provided in the NDA.

- Amend the application with the stated (b) (4) validation file.

Please respond to these requests by no later than **Tuesday, December 27, 2011 at 12:00 pm ET**. Please submit an amendment to your application with your response to the requests using the official channels. To expedite the review process, please send me a courtesy copy through e-mail (Alberta.Davis-Warren@fda.hhs.gov) or FAX (301-796-9849) no later than **Tuesday, December 27, 2011 at 12:00 pm ET**.

Thank you.

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
CDER, FDA

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/s/

ALBERTA E DAVIS WARREN
12/13/2011

FAX



**FOOD AND DRUG ADMINISTRATION
DIVISION OF MEDICAL IMAGING PRODUCTS**

5901-B Ammendale Road
Beltsville, Maryland 20705

To: Rodger A. Brown **From:** Alberta Davis-Warren
FAX/EMAIL RBROWN@neoprobe.com **FAX:** 301-796-9849
Phone: 614-793-7500 **Phone:** 301-796-3908
Pages, including cover sheet: 2 **Date:** November 22, 2011
RE: Information Requests for NDA 202207

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Dear Mr. Brown:

We make reference to your New Drug Application (NDA) for Lymphoseek, and your amendment to the NDA dated November 4, 2011, in which you submitted updated Draft Labeling Text. We have the following clinical information request:

In the new Draft Labeling Text you appear to seek (b) (4)

Please identify or provide the data supporting this claim.

Please respond to these requests by no later than **Thursday, December 22, 2011 at 12:00 pm ET**. Please submit an amendment to your application with your response to the requests using the official channels.

To expedite the review process, please send me a courtesy copy through e-mail (Alberta.Davis-Warren@fda.hhs.gov) or FAX (301-796-9849) no later than **Thursday, December 22, 2011 at 12:00 pm ET**.

Thank you.

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
CDER, FDA

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/s/

ALBERTA E DAVIS WARREN
11/22/2011



NDA 202207

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Neoprobe Corporation
425 Metro Place North, Suite 300
Dublin, Ohio 43017

ATTENTION: Rodger Brown
Vice President, Regulatory Affairs and Quality Assurance

Dear Mr. Brown:

Please refer to your New Drug Application (NDA) dated August 10, 2011, received August 10, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tilmancept for Injection, 0.25 mg per vial.

We also refer to your August 18, 2011, correspondence received August 22, 2011, requesting review of your proposed proprietary name, Lymphoseek. We have completed our review of the proposed proprietary name, Lymphoseek and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your August 22, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sandra Griffith, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Alberta Davis-Warren at (301) 796-3908.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
11/17/2011

Davis-Warren, Alberta E

From: Davis-Warren, Alberta E
Sent: Tuesday, November 15, 2011 3:03 PM
To: 'Brown, Rodger'
Cc: Jerew, Jean
Subject: NDA 202207 Lymphoseek 120 day safety report response

Dear Mr. Brown,

Please see the following comments regarding the (b) (4) 120 day safety report for Lymphoseek:

(b) (4) The FDA Guidance for Industry - E2F Development Safety Update Report (DSUR) is mainly intended for reporting post-market safety updates on approved products. It can also be used for reporting safety updates on ongoing clinical trials conducted under IND. The DSUR is not intended for the 120 day safety report required under 21 CFR during an NDA review.

For your Lymphoseek NDA application, an updated ISS is definitely needed. This cannot be accomplished with a progress report or a DSUR.

With regard to your email inquiry on September 28, 2011:

"One more question on format and impact of the 120 day safety report. Does this include revisions to just the ISS or to all affected modules within the NDA (e.g., modules 1 and 2)? I would expect that if all modules within NDA are changed it would elicit the need for the reviewers to re-review the entire safety profile of the product under the NDA, which could potentially delay the review(?). Can you confirm please?"

If the updated ISS identifies significant new safety signals, you may consider submitting updated Module 2 Clinical Summaries as an NDA amendment. You are correct that submitting an updated ISS during the NDA review cycle would require additional review of the safety components of the submission, and it may elicit the need for the FDA reviewers to re-review the entire safety profile of the product under the NDA. Any NDA amendments submitted before the last 3 months of the NDA review cycle (March 9, 2012 for the Lymphoseek NDA) will not extend the PDUFA date. However if the FDA receives a major NDA amendment during the last 3 months of the NDA review cycle, the PDUFA date can be extended by 3 months.

Please contact me if you have any questions.

Thank you,

Alberta

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
301-796-3908 office
301-796-9849 fax
Alberta.Davis-Warren@fda.hhs.gov

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/s/

ALBERTA E DAVIS WARREN
11/21/2011

FAX

**FOOD AND DRUG ADMINISTRATION
DIVISION OF MEDICAL IMAGING PRODUCTS**

5901-B Ammendale Road
Beltsville, Maryland 20705



To: Rodger A. Brown **From:** Alberta Davis-Warren
FAX/EMAIL RBROWN@neoprobe.com **FAX:** 301-796-9849
Phone: 614-793-7500 **Phone:** 301-796-3908
Pages, including cover sheet: 3 **Date:** November 8, 2011
RE: Information Requests for NDA 202207

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Dear Mr. Brown:

We make reference to your New Drug Application (NDA) for Lymphoseek, submitted on August 10, 2011 under section 505(b) of the Federal Food, Drug, and Cosmetic Act. During our review of the Clinical Pharmacology section of your submission, we have the following Information Requests:

Please summarize what is known regarding:

- 1) plasma pharmacokinetics of technetium Tc 99m tilmanocept;
- 2) total body clearance of technetium Tc 99m tilmanocept;
- 3) routes of elimination (e.g., metabolism) of technetium Tc 99m tilmanocept from the body;
- 4) routes of excretion of technetium Tc 99m tilmanocept;
- 5) plasma pharmacokinetics of metabolites of technetium Tc 99m tilmanocept;
- 6) total body clearance of metabolites of technetium Tc 99m tilmanocept;
- 7) routes of elimination (e.g., further metabolism) of metabolites of technetium Tc 99m tilmanocept from the body; and
- 8) routes of excretion of metabolites of technetium Tc 99m tilmanocept.

For all of the items, we are interested in information obtained following any route of administration to humans. Regarding elimination, we are also interested in *in vitro* data using human biomaterials.

Please respond to these requests by no later than **Tuesday, November 29, 2011 at 12:00 pm ET**. Please submit an amendment to your application with your response to the requests using the official channels.

To expedite the review process, please send me a courtesy copy through e-mail (Alberta.Davis-Warren@fda.hhs.gov) or FAX (301-796-9849) no later than **Tuesday, November 29, 2011 at 12:00 pm ET.**

Thank you.

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
CDER, FDA

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/s/

ALBERTA E DAVIS WARREN
11/08/2011



NDA 202207

FILING COMMUNICATION

Neoprobe Corporation
Attention: Mr. Rodger A. Brown
Vice President, Regulatory Affairs and Quality Assurance
425 Metro Place North
Suite 300
Dublin, Ohio 43017

Dear Mr. Brown:

Please refer to your New Drug Application (NDA) dated August 10, 2011, received August 10, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Lymphoseek (Tilmanocept), powder for injection, 0.25 mg per vial.

We also refer to your amendments dated September 19 and October 7, 2011.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is June 10, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by **April 22, 2012**.

During our filing review of your application, we identified the following potential review issues:

1. Your proposed labeling includes an indication statement that, among other items, claims your drug may be used in the (b) (4)

(b) (4)
[REDACTED]
[REDACTED] you may wish to amend your application to clarify your intentions and to include appropriately revised labeling.

2. Your proposed labeling does not appear to sufficiently describe the clinical use of your drug. [REDACTED] (b) (4)
[REDACTED]. We anticipate a need for you to revise your proposed labeling to provide more explicit directions on how surgeons are to use your drug in the detection of lymph nodes (e.g., describe the potential use of other lymph node mapping agents with your drug, describe the gamma detection procedures used to detected concentrated radioactivity, describe any limitations of your drug in detection of lymph nodes, describe the role of visual inspection and palpation).

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

1. Provide an integrated summary of the risk and benefit assessment. While Module 2.5 Clinical Overview includes a section on risk benefit conclusions, the technical sections of the application lack an integrated summary of the risk and benefit assessment as defined under 21CFR314.50(d)(5)(viii) - "an integrated summary of the benefits and risks of the drug, including a discussion of why the benefits exceed the risks under the conditions stated in the labeling".
2. Provide the coding dictionary used for mapping investigator verbatim terms to preferred terms. The "coding dictionary" consists of a list of all investigator verbatim terms used in safety reporting and the preferred terms to which they were mapped.
3. Provide an integrated summary of your nonclinical study results to support the claim that [REDACTED] (b) (4)
[REDACTED] Please note that this request would not be necessary if you do not intend to make this claim.
4. Provide the USAN name for the radiolabeled drug substance in Lymphoseek. If "Technetium Tc 99m Tilmanocept" is the USAN name, provide confirmation.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. Highlights section needs to be limited in length to one-half page.

2. Highlights Limitation Statement needs to be bolded (i.e., “**These highlights do not...**”).
3. A horizontal line must separate the Table of Contents and Full Prescribing Information.
4. Please italicize all cross referencing see example: *[see Dosage and Administration (2.3)]*

We request that you resubmit labeling that addresses these issues by November 11, 2011. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Alberta Davis-Warren, Regulatory Project Manager, at (301) 796-3908.

Sincerely,

{See appended electronic signature page}

Rafel Dwaine Rieves, M.D.
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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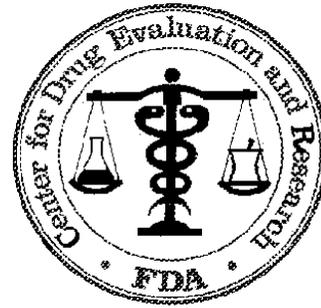
/s/

RAFEL D RIEVES
10/19/2011

FAX

**FOOD AND DRUG ADMINISTRATION
DIVISION OF MEDICAL IMAGING PRODUCTS**

5901-B Ammendale Road
Beltsville, Maryland 20705



To: Rodger A. Brown **From:** Alberta Davis-Warren
FAX/EMAIL RBROWN@neoprobe.com **FAX:** 301-796-9849
Phone: 614-793-7500 **Phone:** 301-796-3908
Pages, including cover sheet: 2 **Date:** October 7, 2011
RE: Information Requests for NDA 202207

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Dear Mr. Brown:

We make reference to your New Drug Application (NDA) for Lymphoseek, submitted on August 10, 2011 under section 505(b) of the Federal Food, Drug, and Cosmetic Act. We also refer to your submission dated October 7, 2011 and we have the following information requests:

Please send the amendment to the NDA including listing datasets and additional navigation from the NEO3-05 and NEO3-09 clinical study reports (CSRs), and the ISS and ISE to these datasets and their corresponding SAS programs as soon as possible and before Friday, October 21, 2011.

Please submit the amendment through the official channels.

Thank you.

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
CDER, FDA

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/s/

ALBERTA E DAVIS WARREN
10/07/2011

MEMORANDUM OF MEETING

DATE: October 5, 2011

APPLICATION NUMBER: NDA 202207 Lymphoseek

BETWEEN: **Neoprobe Corporation:**

Frederick Cope, PhD, Sr. V.P., Pharmaceutical Research and Clinical Development

Rodger Brown, V.P., Regulatory Affairs and Quality Assurance

Wendy Rich Metz ,PhD, Neoprobe Associate Director, Medical Research Review and Development

(b) (4)

Richard McFerron, (called in by Phone)

(b) (4)

AND

Division of Medical Imaging Products, HFD-160

Dwayne Rieves, MD, Director, DMIP (called in)

Louis Marzella, MD, PhD, Deputy Director, DMIP

Alex Gorovets, MD, Clinical Team Leader, DMIP

Brenda Ye, MD, Medical Officer, DMIP

Satish Misra, PhD, Statistical Reviewer, DBI

Gene Williams, PhD, Acting Clinical Pharmacology Team Leader, DCPV

Jared C. Lantzy, Regulatory Information Specialist, OBI

Dhananjay Chhatre, MS, RAC, Operations Research Analyst, OBI

Alberta Davis-Warren, BS, Regulatory Health Project Manager, DMIP

SUBJECT: Missing datasets in the Lymphoseek New Drug Application

HISTORY: On August 10, 2011 Neoprobe Corporation submitted electronically a new drug application for their product Lymphoseek to the Division of Medical Imaging Products. On September 30, 2011 Statistics sent an information request to Neoprobe Corporation requesting they explain the location of certain datasets in the Lymphoseek application during their applicant Orientation meeting being held on October 4, 2011.

The derived efficacy datasets of interest (by study –NEO03-05 and NEO03-09) are:

Node Level:

ID
Demographics
Blue Dye (BD) / Lymphoseek (LS)
Concordance by Node
Pathology Results (+, -, Indeterminate)
BD+, BD -, LS+, LS-, Indeterminate
Hot and Blue both
Hot but not Blue
Blue but not Hot
Neither Blue nor Hot
Reverse Concordance
(Use of Indicator variables is preferred)
Etc.

Patient Level

Concordance
Reverse Concordance
& similar info as above

The applicant provided a response to the information request (see attached), however it did not address Statistical's concerns. Further discussion of the datasets at the orientation meeting prompted an additional meeting to be held the next day on October 5, 2011. Internally prior to the October 5, 2011 meeting, DMIP received assistance from representatives in the Office of Business Informatics (OBI). OBI confirmed that the applicant did not submit the datasets in their new drug application. We sent the following comments to the applicant on October 5, 2011:

FDA IT experts reviewed the validation report and have found no errors indicating that files were included and are not being displayed in the GS Review tool.

The real issue here appears to be confusion about where the efficacy data is located in their submission (?). From working with the FDA statistical reviewer yesterday, the company indicated this data should be in a dataset named "results.xpt" (?). That dataset simply does not exist in the submission either in the GS Review tool, in the individual define.xml files, or from looking at the file/folder structure directly on the server.

The sponsor should verify where they expect us to find the missing efficacy datasets. They should provide a detailed explanation of its location down to the file level, indicating where it should be in the exact file/folder structure.

After receiving this information the applicant realized they have not submitted the requested information in their new drug application.

TODAY'S Meeting:

Mr. Jared Lantzy from OBI gave a demonstration on how to access the information in the system. Mr. Lantzy also discussed that the results.xpt file was missing in the application. Neoprobe explained their process on constructing the datasets (see attached). OBI explained to Neoprobe that the data sets need to be submitted in SAS transport files. Dr. Misra explained to the sponsor that we needed ISE, NEO3-05 and NEO3-09 datasets prior to the end of the business day, Friday, October 7, 2011. Neoprobe agreed to provide this information. Also, as agreed upon with the Division, Neoprobe will provide NEO3-05 and NEO3-09 clinical study reports (CSRs) and the ISS and ISE to these datasets and their corresponding SAS programs at a later time since it will take the company a couple of more weeks to compile this information.

Alberta Davis-Warren, BS
Regulatory Health Project Manager

Response to FDA statistician request for NEO3-05 and NEO3-09 ^a
 Derived Efficacy Dataset Clarifications – 30 SEP 2011

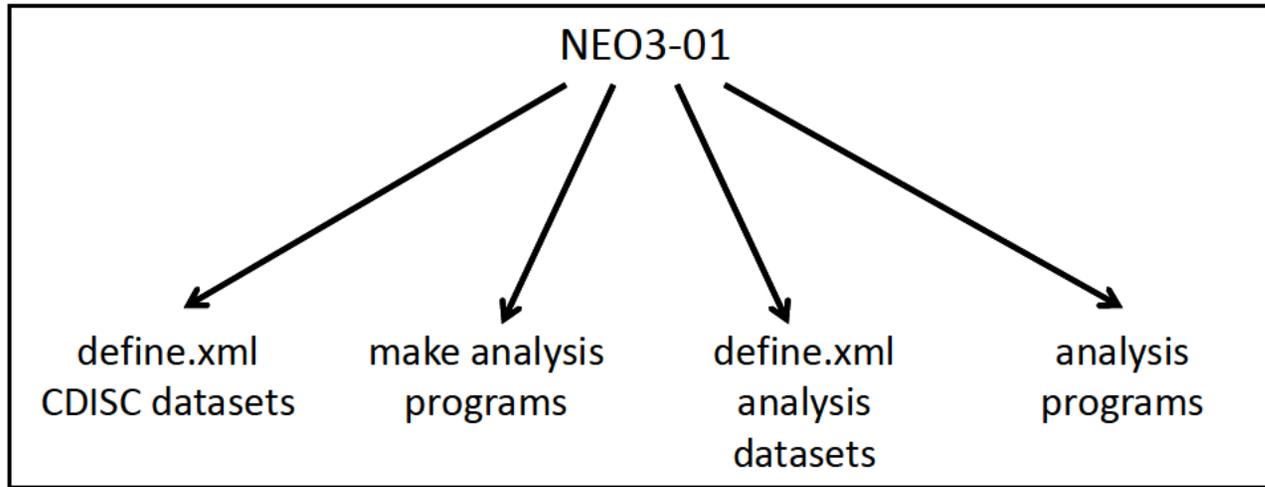
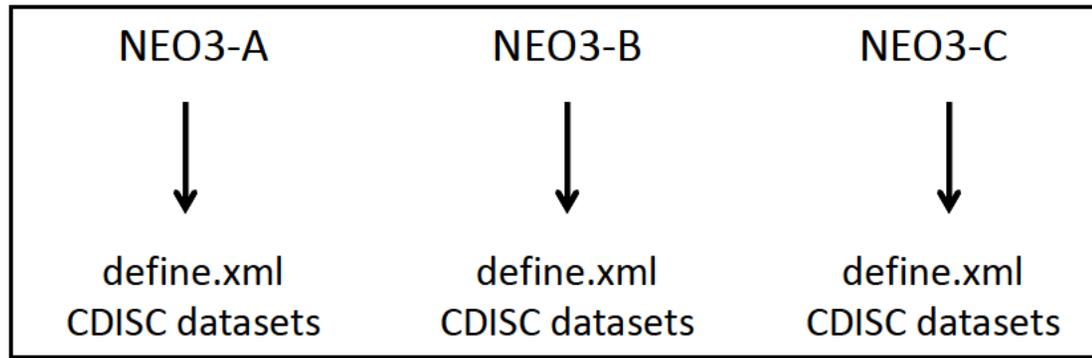
Node Level Variable	Analysis Dataset	SAS Variable Name
ID	Results	NODEID
Concordance	Results	CNCRDID
Pathology	Results	PATHPOS
Blue? (detected by Vital Blue Dye?) ^b	Results	SPECBLUE
Hot? (detected by Lymphoseek?) ^b	Results	SPECDET
Reverse Concordance	Results	RVCRDID

Subject Level Variable	Analysis Dataset	SAS Variable Name
ID	Results	SITESUB
Concordance	Results	CNCRDSUB
Reverse Concordance	Results	RVCRDSUB

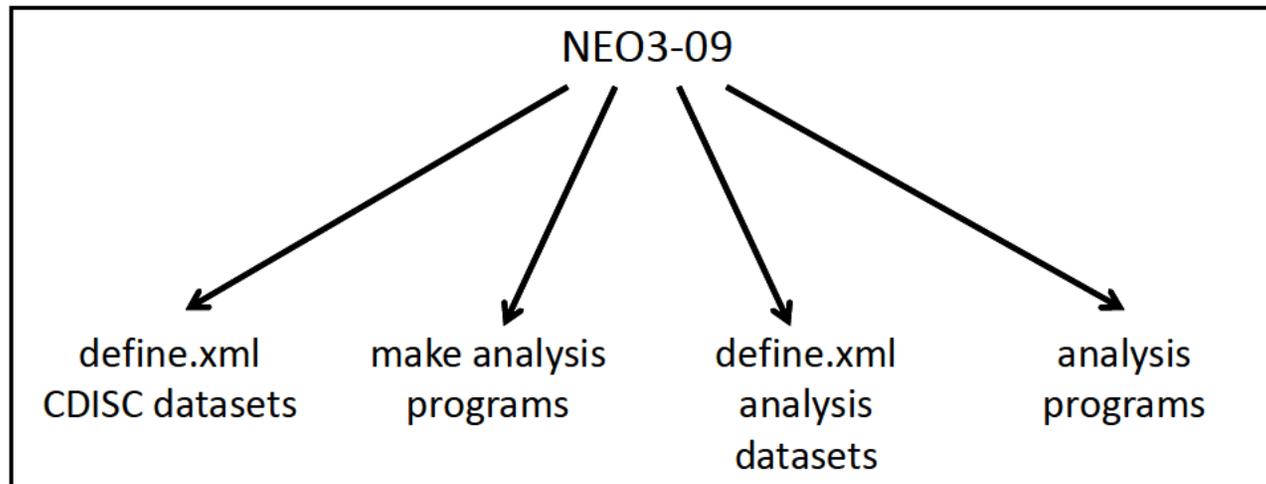
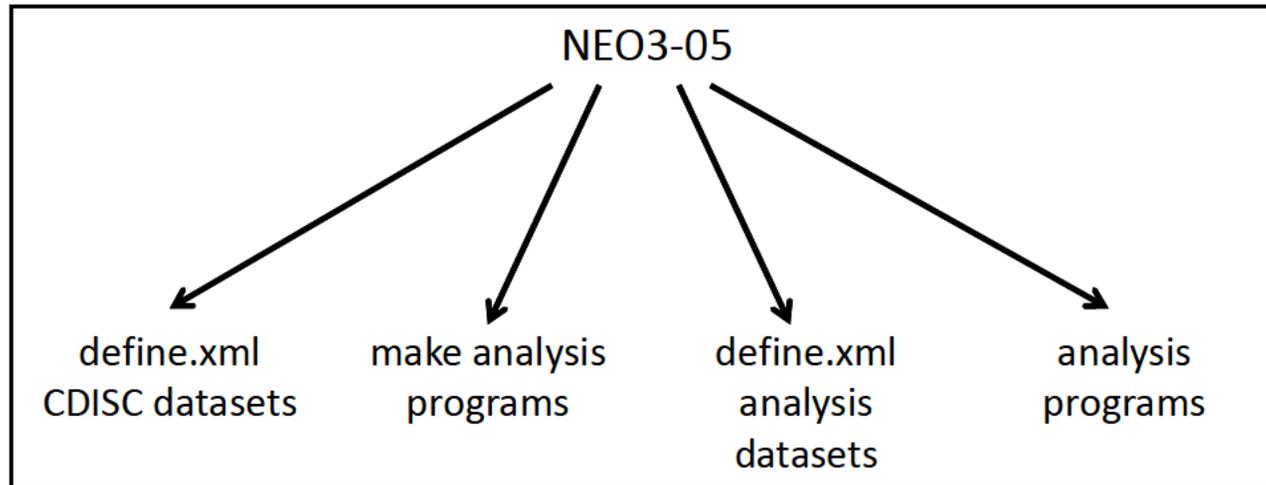
^a All demographics and results data are located in Appendix 16.4 of the individual study reports in Module 5, Section 5.3.5.1.

^b All permutations of hot and blue are covered in these datasets.

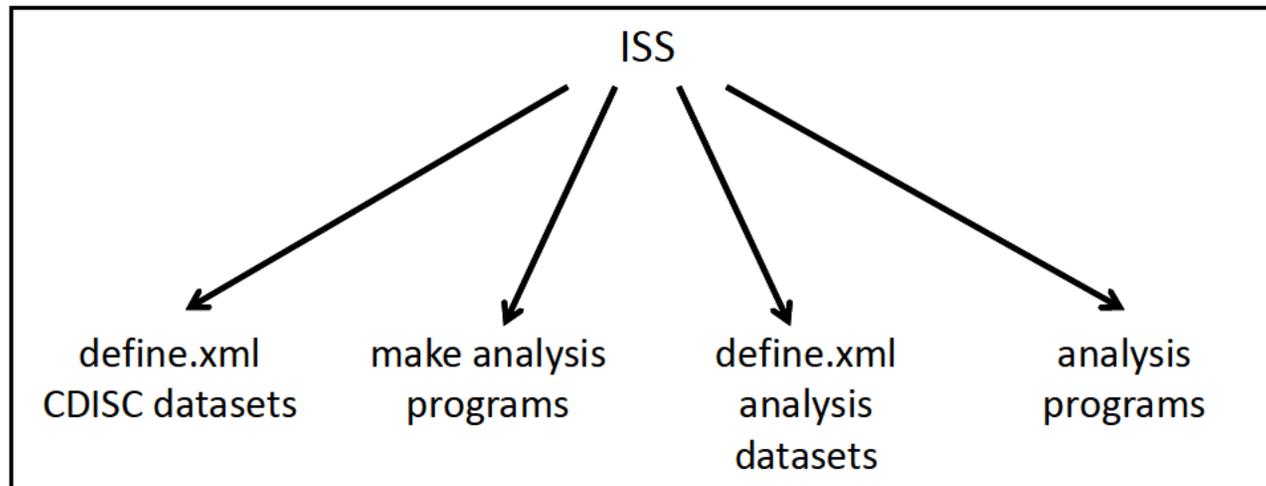
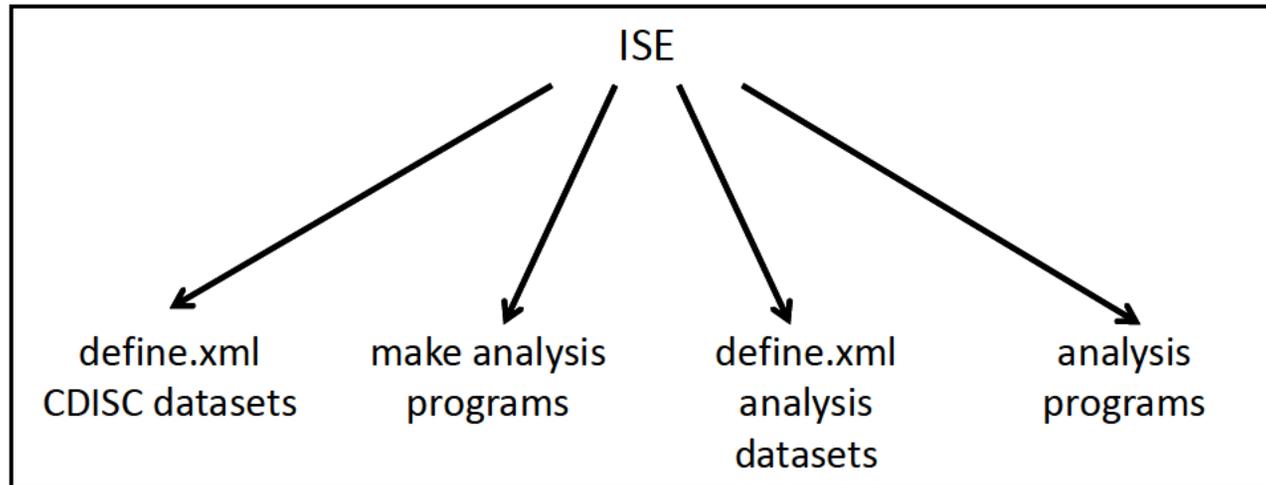
Datasets and SAS Programs by Study
Neoprobe Corporation
October 5, 2011



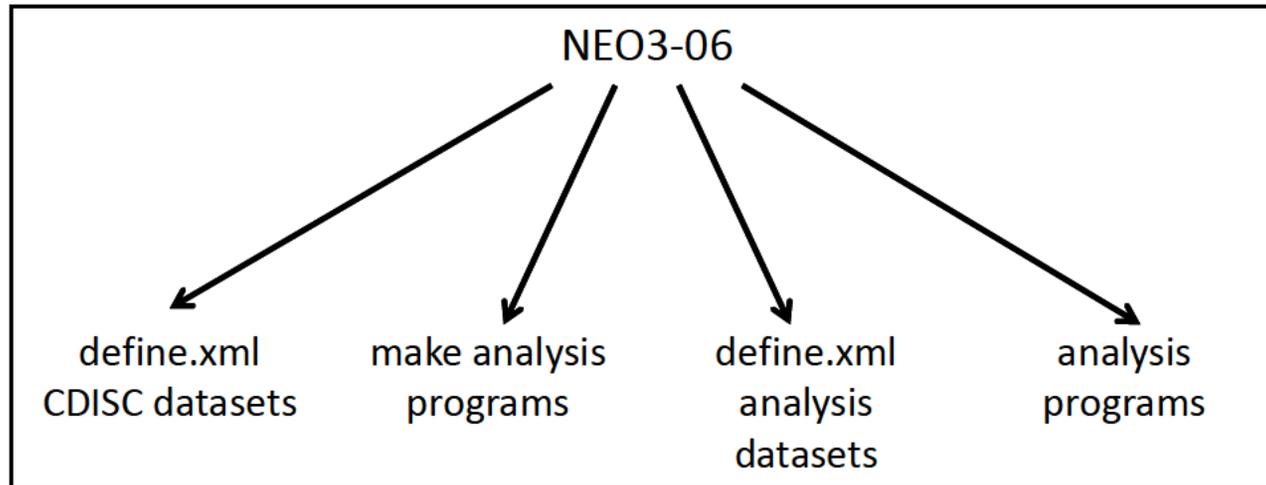
Datasets and SAS Programs by Study
Neoprobe Corporation
October 5, 2011



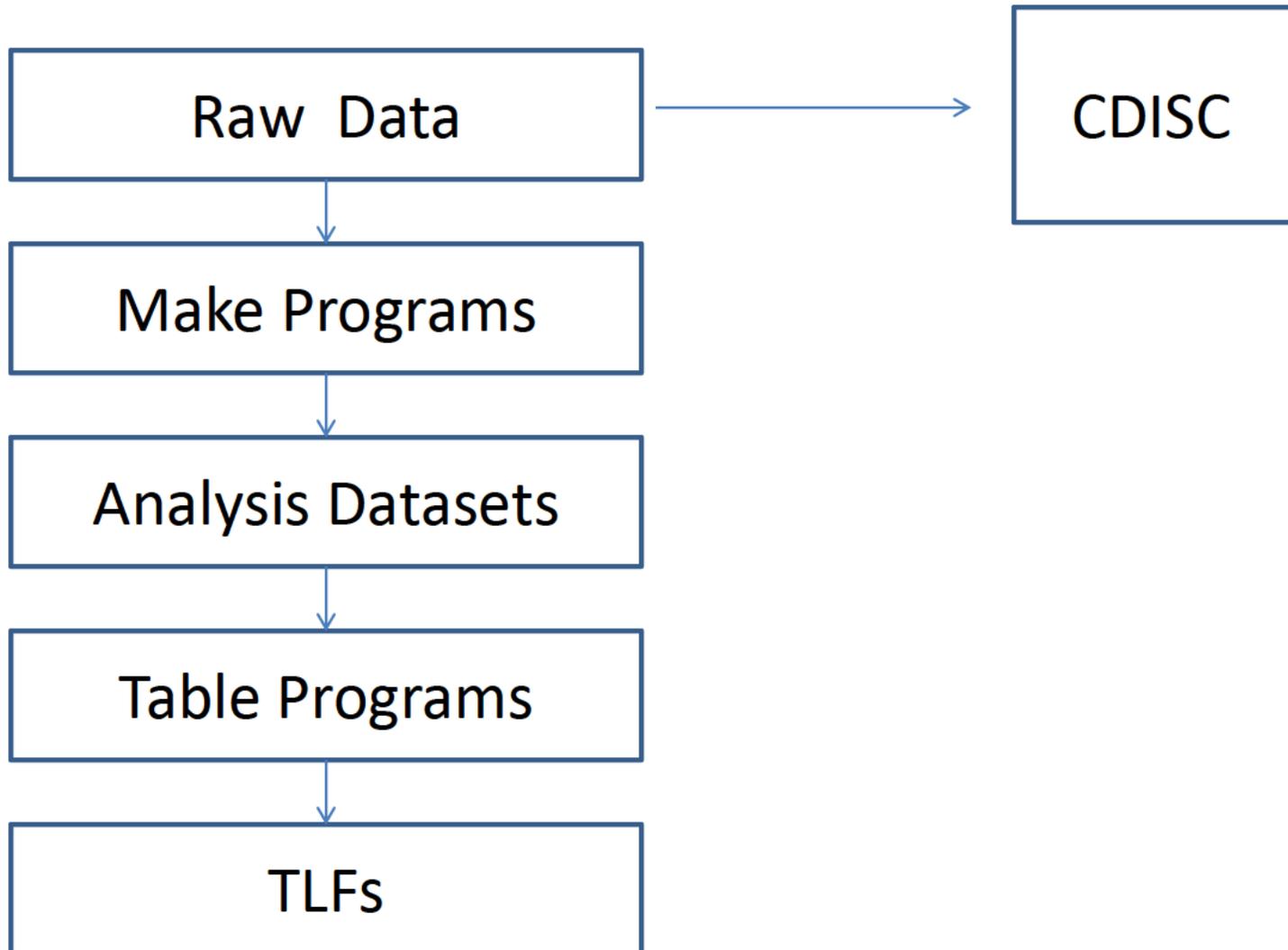
Datasets and SAS Programs by Study
Neoprobe Corporation
October 5, 2011



Datasets and SAS Programs by Study
Neoprobe Corporation
October 5, 2011



Data Flow Diagram



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/s/

ALBERTA E DAVIS WARREN
11/03/2011

Davis-Warren, Alberta E

From: Davis-Warren, Alberta E
Sent: Wednesday, September 28, 2011 2:44 PM
To: 'Brown, Rodger'
Cc: McFerron, Richard; Rich Metz, Wendy
Subject: RE: 120 Day Safety Update Response

Dear Mr. Brown,

Please submit an updated ISS. Please contact me if you have any questions.

Regards,
Alberta

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
301-796-3908 office
301-796-9849 fax
Alberta.Davis-Warren@fda.hhs.gov

From: Brown, Rodger [mailto:RBROWN@neoprobe.com]
Sent: Wednesday, September 21, 2011 10:04 AM
To: Davis-Warren, Alberta E
Cc: McFerron, Richard; Rich Metz, Wendy
Subject: FW: 120 Day Safety Update Response

Dear Ms. Davis-Warren,

Thank you for clarification of the regulations – it is in line with our understanding for the 120-day safety update. Neoprobe is planning on submitting the Lymphoseek 120 day safety update on Thursday, December 8, 2011.

As you mentioned, there is one ongoing study for Lymphoseek (NEO3-06 in head & neck squamous cell carcinoma patients). As discussed previously with the Agency reviewers during the preNDA meeting on October 4, 2010, this is a slow enrolling study and roughly 25 new patients may be included in the safety update (our current ISS database is at 506 patients). There have been no noted Lymphoseek-related safety experiences for these patients in this on-going study. We are aware that submitting a revised ISS during PDUFA may require an additional review of the safety components of the submission. (b) (4)

[REDACTED]

[REDACTED]

Best regards,
Rodger Brown | Vice President, Regulatory Affairs and Quality Assurance
Neoprobe Corporation
425 Metro Place North, Suite 300 | Dublin, OH 43017-1367
Tel: (614) 793-7500
Fax (614) 793-7520
www.neoprobe.com

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/s/

ALBERTA E DAVIS WARREN
09/28/2011

Davis-Warren, Alberta E

From: Davis-Warren, Alberta E
Sent: Tuesday, September 20, 2011 3:39 PM
To: 'Brown, Rodger'
Subject: RE: Questions

Dear Mr. Brown,

Please see the Clinical reviewer's response to your question:

The safety population in your submitted NDA for Lymphoseek is small and one of the clinical studies (NEO3-06) is still ongoing. Therefore it is all the more important for you to provide the 120-day safety update report to the NDA, as required under 21CFR. Please refer to 21CFR314.50(d)(5)(vi)(a) and 21CFR314.50(d)(5)(vi)(b) copied below for further information on the content and format of the report.

(vi) A summary and updates of safety information, as follows:

(a) The applicant shall submit an integrated summary of all available information about the safety of the drug product, including pertinent animal data, demonstrated or potential adverse effects of the drug, clinically significant drug/drug interactions, and other safety considerations, such as data from epidemiological studies of related drugs. The safety data shall be presented by gender, age, and racial subgroups. When appropriate, safety data from other subgroups of the population of patients treated also shall be presented, such as for patients with renal failure or patients with different levels of severity of the disease. A description of any statistical analyses performed in analyzing safety data should also be included, unless already included under paragraph (d)(5)(ii) of this section.

(b) The applicant shall, under section 505(i) of the act, update periodically its pending application with new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling and, if applicable, any Medication Guide required under part 208 of this chapter. These "safety update reports" are required to include the same kinds of information (from clinical studies, animal studies, and other sources) and are required to be submitted in the same format as the integrated summary in paragraph (d)(5)(vi)(a) of this section. In addition, the reports are required to include the case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event (unless this requirement is waived). The applicant shall submit these reports (1) 4 months after the initial submission; (2) in a resubmission following receipt of a complete response letter; and (3) at other times as requested by FDA. Prior to the submission of the first such report, applicants are encouraged to consult with FDA regarding further details on its form and content.

Please contact me if you have any questions.

Thank you,
Alberta

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
301-796-3908 office
301-796-9849 fax
Alberta.Davis-Warren@fda.hhs.gov

-----Original Message-----

From: Brown, Rodger [mailto:RBROWN@neoprobe.com]
Sent: Monday, September 19, 2011 5:14 PM

To: Davis-Warren, Alberta E
Subject: Questions

Dear Ms. Davis-Warren,

The NDA submission clock is running and we have not yet discussed the need for a 120 day safety report. It is my understanding that the FDA will indicate if it is required, and what should be included in the report.

Is a 120 safety report required for Lymphoseek?

Also, if required should it be submitted under the IND or the NDA?

If you have, can we discuss these questions over the telephone?

Best regards,
Rodger Brown | Vice President, Regulatory Affairs and Quality Assurance
Neoprobe Corporation
425 Metro Place North, Suite 300 | Dublin, OH 43017-1367
Tel: (614) 793-7500
Fax (614) 793-7520
www.neoprobe.com

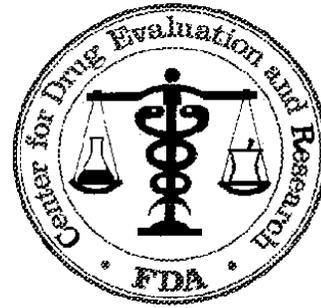
DISCLAIMER: This message contains information which may be confidential or legally privileged. The information is intended to be for the use of the individual or entity addressed to above. If you are not the intended recipient, be aware that any disclosure, copying, distribution or use of the contents of this information is prohibited and may be unlawful.

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/s/

ALBERTA E DAVIS WARREN
09/21/2011

FAX



**FOOD AND DRUG ADMINISTRATION
DIVISION OF MEDICAL IMAGING PRODUCTS**

5901-B Ammendale Road
Beltsville, Maryland 20705

To: Rodger A. Brown **From:** Alberta Davis-Warren
FAX/EMAIL RBROWN@neoprobe.com **FAX:** 301-796-9849
Phone: 614-793-7500 **Phone:** 301-796-3908
Pages, including cover sheet: 2 **Date:** September 8, 2011
RE: Information Requests for NDA 202207

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the address above by mail. Thank you.

Dear Mr. Brown:

We make reference to your New Drug Application (NDA) for Lymphoseek, submitted on August 10, 2011 under section 505(b) of the Federal Food, Drug, and Cosmetic Act. We have the following clinical information requests:

1. Clarify the following information for each study site in Studies NEO3-05 and NEO3-09:
 - Number of patients
 - Number of protocol violations
 - Number of patient withdrawals
 - Number of adverse events and serious adverse events
2. Submit subgroup analyses of efficacy by each study site in Studies NEO3-05 and NEO3-09. Present the analyses separately for the two studies.

Please respond to these requests by no later than **Thursday, September 22, 2011 at 9:00 am ET**. Please submit an amendment to your application with your response to the requests using the official channels. To expedite the review process, please send me a courtesy copy through e-mail (Alberta.Davis-Warren@fda.hhs.gov) or FAX (301-796-9849) no later than **Thursday, September 22, 2011 at 9:00 am ET**.

Thank you.

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
CDER, FDA

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/s/

ALBERTA E DAVIS WARREN
09/08/2011



NDA 202207

NDA ACKNOWLEDGMENT

Neoprobe Corporation
Attention: Rodger A. Brown
Vice President, Regulatory Affairs and Quality Assurance
425 Metro Place North
Suite 300
Dublin, Ohio 43017

Dear Mr. Brown:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Lymphotoseek[®], (Tilmanocept) Powder for Injection, 0.25 mg per vial

Date of Application: August 10, 2011

Date of Receipt: August 10, 2011

Our Reference Number: NDA 202207

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 9, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Medical Imaging Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call me, at (301) 796-3908.

Sincerely,

{See appended electronic signature page}

Alberta Davis-Warren, B.S.
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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

/s/

ALBERTA E DAVIS WARREN
08/18/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 61,757

MEETING MINUTES

Neoprobe Corporation
Attention: Rodger A. Brown
V.P. Regulatory Affairs and Quality Assurance
425 Metro Place North
Suite 300
Dublin, Ohio 43017-1367

Dear Mr. Brown:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Lymphoseek[®].

We also refer to the teleconference between representatives of your firm and the FDA on October 4, 2010. The purpose of the meeting was to discuss the content, format and your preliminary efficacy results to support a New Drug Application (NDA) for Lymphoseek[®].

A copy of the official minutes is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1994.

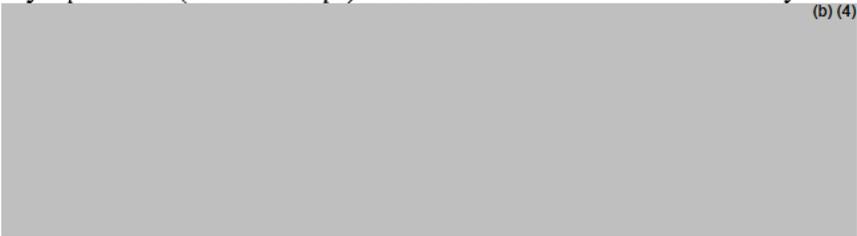
Sincerely,
{See appended electronic signature page}

Sharon Thomas, BS, RHIT, CCRP
Project Management Staff
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure

MEETING MINUTES

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA
Meeting Date and Time: October 4, 2010, 12:00 PM
Meeting Location: White Oak, Conference Room 1421
Application Number: IND 61, 757
Product Name: Lymphoseek (Tilmanocept) Technetium-99m DTPA-mannosyl-dextran
Indication:  (b) (4)

Sponsor/Applicant Name: Neoprobe Corporation

FDA ATTENDEES

Charles Ganley, M.D., Office Director, ODE IV
Rafel Dwaine Rieves, M.D., Division Director, DMIP (*Meeting Chair*)
Libero Marzella, M.D., Ph.D., Clinical Team Leader, DMIP
Brenda Ye, M.D., Clinical Reviewer, DMIP
Adebayo Lanionu, Ph.D., Non Clinical Supervisor, DMIP
Christy John, Ph.D., Clinical Pharmacology Reviewer, OCP
Kasliwal, Ravindra K Ph.D., Chemistry Reviewer, DNDCI
Jyoti Zalkikar, Ph.D., Statistical Team Leader, DBI
Anthony Mucci, Ph.D., Statistical Reviewer, DBI
Sharon Thomas, B.Sc., Regulatory Project Manager, DMIP (*Meeting Recorder*)

SPONSOR ATTENDEES

Frederick Cope, M.D., Sr. VP, Pharmaceutical Research and Clinical Development
David Bupp, President/CEO
George Mills M.D., Consultant, drug development – clinical and regulatory

 (b) (4)
Ann Maloney, Ph.D., Director, Drug Development & Compliance
Wendy Rich Metz, M.D., Assistant Director Clinical Research

BACKGROUND:

On August 6, 2010, the sponsor requested a teleconference to discuss the content, format and preliminary efficacy results to support a New Drug Application (NDA) for Lymphoseek[®], indicated as a radiotracer agent for lymphatic mapping.

On October 1, 2010, the Division provided responses to the sponsor's questions submitted in their briefing package. On October 4, 2010 the sponsor decided to proceed with the scheduled meeting to obtain clarification on the FDA's comments. The discussion is indicated below by *bold italics*.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

Sponsor's Question#1:

Do the results discussed with the Agency on March 2, 2010 provide sufficient information to assess safety and efficacy in support of the NDA?

FDA Response to Question#1:

We remain concerned about the ability of the single confirmatory trial to support a marketing application. The final determination of the sufficiency of the available data ultimately depends on NDA review findings. We encourage you to also submit the safety and efficacy results from at least one of the ongoing phase 3 studies (NEO3-06 and NEO3-09).

NEOPROBE'S RESPONSE:

WE UNDERSTAND FDA'S CONCERN AND ARE COMMITTED TO THE SUBMISSION OF THE NEO3-05 AND THE SECOND PHASE III NEO3-09 STUDY IN ADULT PATIENTS WITH BREAST CANCER OR MELANOMA FOR THE SUBMISSION OF THE NDA AND TO SUPPORT THE MARKETING APPROVAL OF LYMPHOSEEK.

THE THIRD PHASE III STUDY NEO3-06 IS A LONG TERM ENROLLING STUDY ANTICIPATED FOR COMPLETION OF ENROLLMENT IN Q2, 2012. NEO3-06 WAS PREVIOUSLY NOTED TO THE AGENCY AS NOT INTENDED TO BE PART OF THE PRIMARY NDA SUBMISSION (SEE MARCH 2, 2010 MINUTES, NEOPROBE AND FDA, TYPE C MEETING). NEOPROBE IS ANTICIPATING REVIEWING THE STUDY EFFICACY RESULTS THROUGH 2012. NEOPROBE WILL ASSESS THE SAFETY DATABASE (CURRENTLY 22 PATIENTS ARE COMPLETED) AND WILL PROVIDE A SAFETY UPDATE IN THE PRIMARY NDA SUBMISSION FROM THE COMPLETED PATIENTS IN THE NDA. WE WILL INCLUDE ALL PATIENTS COMPLETED 60 DAYS PRIOR TO THE NDA SUBMISSION.

NEO3-06

(b) (4)

EFFICACY FINDING
ARE NOT INTENDED TO BE INCLUDED IN THE PRIMARY NDA SUBMISSION.

DISCUSSION:

FDA noted that the sponsor had changed their position in regard to the primary submission and requested the safety and efficacy data from the NEO3 -09 study. The sponsor concurred.

Sponsor's Question#2:

Is the proposal to amend the NDA safety database with additional data from the Phase III study NEO3-09 acceptable as discussed with the FDA review team in March 2, 2010?

FDA Response to Question#2:

No, this is not acceptable. We cannot accept a partially completed NDA submission. This is especially the case where the proposed safety database appears relatively small in number. You state that three hundred and sixty-six (366) patients have received Lymphoseek, and an additional 139 patients (total 505 patients) are anticipated to have received Lymphoseek by April 2011. We regard the total of 505 patient-exposure sample size as a relatively small safety database; hence submission of even fewer patients with the original NDA presents a particular challenge. We encourage you to submit the NDA after receiving the complete safety data from the 505 patients.

NEOPROBE'S RESPONSE:

NEOPROBE WILL PROVIDE THE TWO COMPLETED PHASE 3, ADEQUATE AND WELL CONTROLLED TRIALS TO THE PRIMARY NDA SUBMISSION (NE03-05 AND NEO3-09).

NEOPROBE CONFIRMS THAT THE COMPLETION OF THE TWO ADEQUATE AND WELL CONTROLLED STUDIES. NEOPROBE WILL PROVIDE AT LEAST 505 COMPLETED ADULT SUBJECTS FOR SAFETY. IN THIS REGARD, NEOPROBE WILL PROVIDE THE SAFETY RESULTS FROM PATIENTS COMPLETED IN NEO3-06, 60 DAYS PRIOR TO THE PRIMARY NDA SUBMISSION FOR LYMPHOSEEK (SEE RESPONSE TO QUESTION 1, ABOVE).

DISCUSSION:

There was no further discussion on this question.

Sponsor's Question#3:

Does FDA accept that this proposal will be supportive for their review of the efficacy determination and will support the NDA?

FDA Response to Question#3:

We remain concerned about the ability of the one phase 3 trial along with the phase 2 trial to support the efficacy expectations of a marketing application. As noted above, the ultimate determination of sufficiency depends on review findings. In addition, have the Agency's requested additional efficacy analyses discussed at the EOP3 meeting been completed and submitted?

NEOPROBE'S RESPONSE:

NEOPROBE WILL PROVIDE THE TWO COMPLETED PHASE 3, ADEQUATE AND WELL CONTROLLED TRIALS TO THE PRIMARY NDA SUBMISSION (NE03-05 AND NEO3-09).

NEOPROBE HAS COMPLETED THE EFFICACY ANALYSES OF NEO3-05, AS REQUESTED IN THE MARCH 2ND MEETING. THESE HAVE BEEN SUBMITTED (AMENDMENT NUMBERS 0048 AND 0066) TO THE IND 61757 AND WILL BE SUBMITTED IN THE EFFICACY ANALYSIS WITHIN THE NDA.

DISCUSSION:

There was no further discussion on this question.

Nonclinical

Sponsor's Question#4:

Is there sufficient nonclinical study data to support the proposed NDA?

FDA Response to Question#4:

There appears to be the appropriate nonclinical studies to support the review of the proposed NDA. However, during the conduct of critical nonclinical and clinical reviews there may be issues that become apparent that may require further evaluation.

NEOPROBE'S RESPONSE:

WE APPRECIATE FDA'S DUE DILIGENCE IN ASSESSING THE ADEQUACY OF ALL INFORMATION AND DATA PROVIDED BY NEOPROBE IN THE PROPOSED NDA 202207.

DISCUSSION:

There was no further discussion on this question.

Sponsor's Question#5:

In the context of the Nonclinical testing, the Sponsor proposes to request waivers for carcinogenesis, reproductive, and metabolite/impurity testing (see Attachments 7, 8, and 9, respectively; NOTE: Neoprobe has had these waivers reviewed by outside experts in the areas of reproductive toxicology, carcinogenesis, and drug metabolism; these letters are attached to the waivers). Is this acceptable to the FDA?

FDA Response to Question#5:

- 1. The request for waivers of carcinogenesis and reproductive testing appears to be a reasonable proposal.**

NEOPROBE'S RESPONSE:

THANK YOU; ALL PERTINENT INFORMATION AND DATA REGARDING THIS WAIVER ARE INCLUDED IN THE PROPOSED NDA 202207.

DISCUSSION:

There was no further discussion on this question.

- 2. Your request for a waiver of metabolite testing is a review issue and will be determined by the quality of the justification information. The opinions of the outside experts will be considered during the critical review of the NDA.**

NEOPROBE'S RESPONSE:

THANK YOU; ALL PERTINENT INFORMATION AND DATA REGARDING THIS WAIVER ARE INCLUDED IN THE PROPOSED NDA 202207.

DISCUSSION:

There was no further discussion on this question.

- 3. Your request for a waiver of impurity testing is not acceptable. We were unable to determine the composition and impurity profile of the product used for your genotoxicity and general toxicology studies and compare them to the profile of the "to be marketed" formulation. We will work closely with our CMC colleagues in arriving at a determination of the need for additional nonclinical impurities testing. Please refer to the following Guidances**

Guidance for Industry: ICH Q3A (Revision 2) impurities in new drug substances

Guidance for Industry: Genotoxic and carcinogenic impurities in drug substances: Recommended Approaches.

NEOPROBE'S RESPONSE:

FOLLOWING DISCUSSIONS WITH THE AGENCY AND IN AGREEMENT WITH THE AGENCY ON MAY 8, 2007, NEOPROBE COMPLETED BRIDGING STUDIES BETWEEN THE PRODUCT USED FOR GENOTOXICITY AND GENERAL TOXICOLOGY STUDIES AND THE TO BE MARKETED PRODUCT IN 2007. NEOPROBE ADDRESSED THE IMPURITY PROFILE OF THE PRODUCT USED FOR THE GENOTOXICITY AND GENERAL TOXICITY STUDIES THROUGH BRIDGING STUDIES IN 2006, AND SUBMITTED THE RESULTS (AMENDMENT 0015) OF THE BRIDGING STUDIES UNDER IND 61757 (2007).

DISCUSSION:

There was no further discussion on this question.

Other General Questions

Neoprobe: The proposed NDA will be outlined and submitted electronically in accordance with current eCTD guidance (ICH) and Agency regulations (Guidance for Industry Submitting Marketing Applications According to the ICH-CTD Format - General Considerations - 2009). Clinical and nonclinical data will be provided in SAS / CDISK compliant formats, where applicable.

Sponsor's Question#6:

Is an electronic CTD (the NDA) in the prescribed ICH structure for the presentation of data sufficient for the NDA?

FDA Response to Question#6:

Yes.

NEOPROBE'S RESPONSE:

THANK YOU, THE PROPOSED NDA WILL COMPLY WITH THIS REQUIREMENT. FDA HAS RECENTLY CONFIRMED THE ESG ACCESS FOR NEOPROBE.

DISCUSSION:

There was no further discussion on this question.

Pediatric Safety and Effectiveness

Neoprobe Corporation is planning to request a pediatric waiver based on the information previously provided in IND 61757-0051. In accordance with the Pediatric Research Equity Act (Public Law 108-155) (PREA), and as it amends the Federal Food, Drug, and Cosmetic Act (the Act) by adding section 505B (21U.S.C. 355B), and per Section 505B(a)(4)(A) of the Act, we are planning to a request a Full Waiver in all pediatric ages (< 18 years) regarding the intended use of Lymphoseek® (Kit for the Preparation of Technetium Tc 99m DTPA Mannosyl Dextran for Injection) with a proposed indication for (b) (4). Neoprobe believes that the proposed indications for Lymphoseek would be rare or nonexistent. The imposition of clinical trials in pediatric age groups is not justified at this time and would unduly delay the adoption of Lymphoseek in this fragile population that may benefit from its use.

Sponsor's Question#7:

Is the proposal to request a pediatric waiver acceptable?

FDA Response to Question#7:

While you may request a waiver, we do not believe the intended use of Lymphoseek for lymphoid tissue (b) (4) is a rare or nonexistent clinical indication in the entire pediatric ages (<18 years). While breast cancer or melanoma may be rare in the pediatric population, there are other oncologic conditions in the pediatric population that lymphatic mapping procedures may be indicated.

NEOPROBE'S RESPONSE:

NEOPROBE WILL REQUEST A PEDIATRIC WAIVER IN THE NDA SUBMISSION. NEOPROBE WILL WORK WITH THE AGENCY TO CONSIDER POTENTIAL PEDIATRIC CLINICAL TRIALS, IF THE AGENCY REQUIRES A DEFERRAL OF PEDIATRIC CLINICAL TRIALS RATHER THAN ACCEPTING NEOPROBE'S PEDIATRIC WAIVER APPLICATION.

WE HAVE CONTACTED THREE MAJOR CHILDREN'S CENTERS IN THE U.S.A. AND ASSESSED THE CURRENT FREQUENCY OF OCCURRENCE IN ALL CANCER TYPES OCCURRING IN THE PEDIATRIC POPULATIONS. FOR THE TWO PROPOSED INDICATIONS FOR ADULT PATIENTS, BREAST CANCER AND MELANOMA, BOTH

ARE CONSIDERED TO BE RARE AND SUFFICIENT PEDIATRIC PATIENTS ARE NOT AVAILABLE FOR ADEQUATE AND WELL CONTROLLED TRIALS. NEOPROBE WOULD BE WILLING TO EXPLORE WITH THE AGENCY OTHER POTENTIAL INVESTIGATIONAL APPLICATIONS OF LYMPHOSEEK IN THE PEDIATRIC POPULATION. HOWEVER, THE POTENTIAL POPULATIONS FOR ENROLLMENT FOR SUCH OTHER APPLICATIONS MAY BE MINIMAL TO SUPPORT ADEQUATE AND WELL CONTROLLED CLINICAL TRIALS THAT CAN BE COMPLETED IN A TIMELY FASHION.

DISCUSSION:

There was no further discussion on this question.

Proprietary name:

“Lymphoseek[®]” was developed and used during the clinical development of the product by UCSD and Neoprobe. Neoprobe has subsequently applied for, but has yet to receive confirmation of the Proprietary Name “Lymphoseek[®]k”.

Generic name [USAN]:

Neoprobe Corporation has applied for, and has received the USAN “technetium Tc 99m tilmanocept”. Other names used in conjunction with this product: “Lymphoseek[®]: Kit for the Preparation of Technetium Tc 99m DTPA Mannosyl Dextran for Injection” was developed and used during the clinical development of the product. Neoprobe has recently received the USAN (generic name) and has updated that naming convention accordingly. We now identify the cold radiopharmaceutical kit as “Lymphoseek[®]: Kit for the Preparation of Technetium Tc 99m Tilmanocept for Injection”. Neoprobe has filed “Lymphoseek[®]” as a registered trademark with the U.S. Patent and Trademark Office and has received clearance for the registered trademark Lymphoseek[®].

Sponsor’s Question#8:

Does the FDA agree with the proposed Proprietary Name for the product?

FDA Response to Question#8:

If you have submitted a proposed propriety name for review, you will receive notification of the review result from FDA’s Office of Surveillance and Epidemiology.

NEOPROBE’S RESPONSE:

THANK YOU FOR THE CLARIFICATION AND DIRECTION.

DISCUSSION:

There was no further discussion on this question.

Submission review timeline:

Neoprobe: Current radiopharmaceuticals are being used off-label in lymphatic mapping surgeries. Neoprobe Corporation believes that there is an unmet need for a safe and effective

“on-label” radiopharmaceutical such as Lymphoseek[®] and requests that FDA consider expedited review of the Lymphoseek[®] application.

Sponsor’s Question#9:

Would FDA consider expedited review of the NDA for Lymphoseek[®] at this time?

FDA Response to Question#9:

Other imaging agents are available for lymphatic mapping procedures. We do not perceive that Lymphoseek[®] has the potential to address an unmet medical need for imaging agents in lymphatic mapping procedures. Designation of review timeline will be made at the NDA filing review, and will be conveyed via the NDA 74-day letter.

NEOPROBE’S RESPONSE:

THANK YOU FOR THE FOR ADDRESSING THIS QUESTION; NO ADDITIONAL DISCUSSION IS REQUIRED.

DISCUSSION:

There was no further discussion on this question.

Patent Protection:

Neoprobe: An applicant shall submit with its original application each drug (ingredient), drug product (formulation and composition), and method of use patent issued before the application is filed with FDA. Neoprobe Corporation is submitting patent information for the new drug Lymphoseek[®] in accordance with 21 CFR 314.53 Submission of patent information for drug substance (active ingredient) patents, drug product (formulation and composition) patents, and method-of-use patents.

Sponsor’s Question#10:

Will the new drug Lymphoseek[®] qualify for patent protection?

FDA Response to Question#10:

Patents and marketing exclusivity are distinctly different subjects. Patents are granted by the US Patent and Trademark office. Exclusivity refers to marketing rights granted by the FDA. Additional information is available at the FDA website (place “Frequently Asked Questions on Patents and Exclusivity” within the search box at www.fda.gov).

NEOPROBE’S RESPONSE:

AGREED; WE BELIEVE THAT LYMPHOSEEK[®] DOES QUALIFY FOR MARKETING EXCLUSIVITY WITH REGARD TO 21 CFR SEC. 314.108 NEW DRUG PRODUCT EXCLUSIVITY. WE RESPECTFULLY REQUEST THAT FDA CONSIDER LYMPHOSEEK[®] FOR MARKETING EXCLUSIVITY. THE REQUEST FOR EXCLUSIVITY IS TO BE INCLUDED IN THE NDA MODULE 1; SECTION 1.3.5 THE FORM FDA 3542, PATENT INFORMATION SUBMITTED UPON AND AFTER APPROVAL OF AN NDA OR SUPPLEMENT IS TO BE INCLUDED IN THE NDA FOR LYMPHOSEEK[®]; MODULE 1; SECTION 1.3.5.1

DISCUSSION:

There was no further discussion on this question.

Advisory Committee Review:

Neoprobe understands that Lymphoseek[®] is a new chemical entity. Therefore it is anticipated that Lymphoseek[®] may be reviewed by an FDA advisory committee.

Sponsor's Question#11:

Which advisory committee does FDA anticipate will review Lymphoseek[®]; will it be the newly designated medical imaging advisory committee?

FDA Response to Question#11:

We anticipate the Lymphoseek[®] NDA to be discussed by an FDA advisory committee with the necessary medical imaging expertise. The specific advisory committee will be designated during the NDA review, if an advisory committee is proposed. Please be aware that the determination of the need for an advisory committee discussion is made following preliminary review of the NDA application.

NEOPROBE'S RESPONSE:

THANK YOU FOR ADDRESSING THIS QUESTION. NEOPROBE UNDERSTANDS THIS REQUIREMENT AND AWAITS FINAL DETERMINATION.

DISCUSSION:

There was no further discussion on this question.

CMC

Sponsor's Question#12:

Is the proposed statistical methodology adequate to support the submission of the NDA?

FDA Response to Question#12:

Yes, from a preliminary assessment of the proposal. The proposal will be consulted for a detailed and definitive statistics review. If there are any concerns or any aspects for which advice is provided from the consult, it will be conveyed to the firm.

NEOPROBE'S RESPONSE:

THANK YOU FOR THE CLARIFICATION. NEOPROBE UNDERSTANDS THIS REQUIREMENT AND AWAITS FINAL DETERMINATION.

DISCUSSION:

There was no further discussion on this question.

Environmental Assessment:

Neoprobe Corporation plans to request environmental exclusion based on the environmental assessments performed to date.

Sponsor's Question#13:
Does FDA agree with the proposed environmental exclusion plan?

FDA Response to Question#13:

All previous assessments should be provided in the NDA. However, be aware that in support of a request for exclusion a numerical estimate of the concentration of the substance at the point of entry into the aquatic environment should be below 1 ppb (21 CFR 25.31(b)). You can find the appropriate procedure for making this estimate in the following FDA guidance.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070561.pdf>.

NEOPROBE'S RESPONSE:

THANK YOU. WE HAVE COMPLETED THE ENVIRONMENTAL ASSESSMENT IN COMPLIANCE WITH THESE STATED REQUIREMENTS AND THE RESULTS ARE TO BE INCLUDED IN THE NDA MODULE 1; SECTION 1.12.4.

DISCUSSION:

There was no further discussion on this question.



(b) (4)

(b) (4)



INSTRUCTIONS, FORMS AND RECORDS). WE LOOK FORWARD TO FDA'S ASSESSMENT.

DISCUSSION:

There was no further discussion on this question.

General Information:

Sponsor's Question#15:

Does the FDA agree that the plans and information provided in this preNDA meeting request adequately addresses the Agency's expectations for pursuing a new drug application (NDA) in the following areas?

- Chemistry, Manufacturing and Controls (CMC)
- Pharmacology
- Pharmacokinetic
- Microbiology
- Clinical Data
- Risk
- Safety
- Pharmacovigilance

FDA Response to Question#15:

Please see our comments above and our response to Question 18.

NEOPROBE'S RESPONSE:

NEOPROBE NOTES YOUR RESPONSE TO QUESTION 18.

DISCUSSION:

See discussion point below to Question 18.

21 CFR Part 208 prescribes a Medication Guide for Prescription Drugs.

Sec. 208.26 Exemptions and deferrals. (a) FDA on its own initiative, or in response to a written request from an applicant, may exempt or defer any medication guide content or format requirement, except those requirements in 208.20 (a)(2) and (a)(6), on the basis that the requirement is inapplicable, unnecessary, or contrary to patients' best interests. Requests from applicants should be submitted to the director of the FDA division responsible for reviewing the marketing application for the drug product, or for a biological product, to the application division in the office with product responsibility. Lymphoseek[®] is intended to be administered by, or under the direct supervision of a healthcare professional, not by a patient. Additionally, based on the results of nonclinical testing, environmental assessment, clinical studies, and proposed indication for use (claim), we do not believe that Lymphoseek[®] poses a serious and significant public health concern as defined in 21 CFR 208.1 Scope and Purpose of this section of the Act, or as defined in 21 CFR 314.104 of the Act for drugs with potential for abuse. Neoprobe proposes to request an exemption in accordance with 21 CFR 208.26 of this section of the Act.

Sponsor's Question#16:

Does FDA agree to the proposed Exemption from this Medication Guide requirement except those requirements in 208.20 (a)(2) and (a)(6)?

FDA Response to Question#16:

We do not anticipate the need for a medication guide for this product and a request for exemption is not needed.

NEOPROBE'S RESPONSE:

THANK YOU FOR THE CLARIFICATION. WE WILL REMOVE THIS REQUEST FROM THE NDA MODULE 1; SECTION 1.14

DISCUSSION:

There was no further discussion on this question.

Neoprobe: The regulation requires the submission of a safety report 4months following the Application filing date. The regulation states that the applicant needs to request the format and content of the safety report from the reviewing division.

Sponsor's Question#17:

Can FDA provide the format and content requirements for the 4 month safety report?

FDA Response to Question#17:

We refer you to 21 CFR 314.50 (d)(5)(vi)(a) and 314.50 (d)(5)(vi)(b). Present the data as an integrated summary of safety. Include information from clinical studies, animal studies, literature and other reporting sources. If warranted by the numbers, summarize the data by gender, age, racial subgroups, severity of reactions and severity of underlying disease. Include a description of analysis methodology of applicable.

NEOPROBE'S RESPONSE:

THANK YOU FOR THE CLARIFICATION AND DIRECTION. WE WILL PROVIDE THE INFORMATION IN THE FORMAT INDICATED.

DISCUSSION:

There was no further discussion on this question.

Neoprobe: We believe the information contained in this briefing document address the Agency's expectations for filing the Application.

Sponsor's Question#18:

Is there additional information, apart from that provided herein that the FDA would require for the proposed Application?

FDA Response to Question#18:

1) We request that you provide the additional analyses discussed at the EOP3 meeting on March 2, 2010:

“The primary endpoint of the protocol, concordance, is really Lymphoseek[®] sensitivity with respect to Blue Dye. That is, it measures the extent to which Lymphoseek also finds lymph nodes found by Blue Dye. This places Blue Dye in the position of a Truth Standard and ignores the possibility that Lymphoseek[®] might identify more lymph nodes than Blue Dye. The secondary analyses you have performed explored this possibility.

Based on this premise, we would like you to perform the following additional secondary exploratory analyses:

Collect all tissue samples found by either Lymphoseek[®] or Blue Dye, or by other means, and determine which are actually lymph nodes, and then examine the table of frequencies of four outcomes over this sample. Entries are:

Found by Both

Found by Neither

Found by Blue Dye, not by Lymphoseek[®]

Found by Lymphoseek, not by Blue Dye

The comparison of interest would be:

% found by Blue Dye, not by Lymphoseek[®] vs. % found by Lymphoseek, not by Blue Dye

This examines the comparative ability of blue dye and Lymphoseek[®] to detect lymph nodes.”

NEOPROBE’S RESPONSE:

NEOPROBE HAS COMPLETED THESE SUPPLEMENTAL ANALYSES THAT WERE DISCUSSED IN THE MARCH 2, 2010 MEETING. THE RESULTS OF THESE ANALYSES ARE INCLUDED IN THE MINUTES OF MARCH 2, 2010 MEETING WITH THE AGENCY (AMENDMENTS 0048 AND 0066) AND WILL BE SUBMITTED TO THE IND 61757 AS A SEPARATE AMENDMENT. NEOPROBE WILL SUBMIT THESE RESULTS IN THE NDA.

NEOPROBE HAS PERFORMED THE ADDITIONAL SECONDARY EXPLORATORY ANALYSES FOR NEO3-05 REQUESTED BY THE AGENCY. THESE RESULTS ARE IN THE MINUTES OF THE MARCH 2, 2010 MEETING. THESE RESULTS WILL BE SUBMITTED AS A SEPARATE AMENDMENT TO IND 61757. IN REFERENCE TO THE ONGOING NEO3-09 TRIAL, THESE REQUESTED ANALYSES ARE A PROSPECTIVE COMPONENT OF THE STATISTICAL ANALYSIS PLAN FOR THIS STUDY, AND THESE RESULTS WILL BE SUBMITTED UNDER THE NDA. THESE ANALYSES ARE ALSO A PROSPECTIVE COMPONENT OF THE STATISTICAL ANALYSIS PLAN FOR THE INTEGRATED EFFICACY SUMMARY OF THE NDA AND WILL BE SUBMITTED UNDER THE NDA.

2) We cannot accept your proposal of a ‘planned’ major amendment prior to the NDA submission. We request that you include the safety data from study 06 and study 09 in your initial NDA submission.

NEOPROBE'S RESPONSE:

NEOPROBE DOES NOT INTEND TO HAVE A PLANNED MAJOR AMENDMENT TO THE NDA SUBMISSION. SEE COMMENTS AND REPLIES IN QUESTIONS 1, 2 AND 3 ABOVE.

3) Please clarify the regulatory status of the imaging devices that are intended to be used with Lymphoseek[®], such as handheld gamma probe, gamma cameras, etc. Confirm that all these devices have been marketed based upon FDA approval or clearance.

NEOPROBE'S RESPONSE:

BASED ON NEOPROBE'S CLINICAL RECORDS FROM NEO3-05, NEO3-09, AND NEO3-06, ALL GAMMA CAMERAS USED AS A PRESURGICAL ADJUNCT TO THE INTRAOPERATIVE PROBING IN THE CONDUCT OF THE CLINICAL TRIALS WERE COMMERCIALY AVAILABLE UNITS AND, AS SUCH, CLEARED BY FDA/CDRH FOR IMAGING Tc 99m.

NEOPROBE WILL PROVIDE A TABLE LISTING THE FIVE COMMERCIALY AVAILABLE CDRH-CLEARED GAMMA DETECTION PROBES (21 CFR 892.1320 NUCLEAR UPTAKE PROBE) UTILIZED IN THE NEO3-05, NEO3-09, AND NEO3-06 TRIALS SPONSORED BY NEOPROBE.

Discussion:

FDA requested that the sponsor provide the 510K numbers assigned to the probes. The sponsor concurred.

4) The pathologically positive lymph nodes appear to represent a relatively small percentage of the lymph nodes that were excised in the clinical studies. The NDA submission needs to contain discussions on whether this is expected in the target patient population of Lymphoseek[®]. Submit results of literature review as needed.

NEOPROBE'S RESPONSE:

THE INFORMATION REQUESTED WILL BE PROVIDED IN THE NDA SUBMISSION.

5) The NDA submission needs to contain pathology results of each excised node and whether the submitted tissue specimen was identified as lymphoid tissue by pathology. Incorporate these results in tabular presentations of efficacy results. For example, the format used in Table 11 of the phase 2 study report (NEO3-01) might be considered.

NEOPROBE'S RESPONSE:

THE DATA FROM PHASE III CLINICAL STUDIES NEO3-05 AND NEO3-09 STUDIES SPONSORED BY NEOPROBE, INCLUDING THE DISEASES BREAST CANCER, MELANOMA, *PROVIDE FOR THE PATHOLOGY AND HISTOLOGICAL EVALUATIONS OF*

ALL SURGICALLY RESECTED TISSUES REMOVED FROM PATIENTS. THESE DATA WILL BE INCLUDED IN THE NDA.

THE NDA SUBMISSION WILL CONTAIN THE PATHOLOGY EXAMINATION RESULTS OF EACH TISSUE SPECIMEN EXCISED AS A POTENTIAL LYMPH NODE.

6) The NDA submission needs to document the time interval between Lymphoseek[®] injection (and blue dye injection for NEO3-05) and intraoperative lymphatic mapping (ILM) for each subject as part of the efficacy results.

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- c) **Document the time interval between Lymphoseek[®] injection and in vivo counting and ex vivo counting of lymph nodes for each patient in the NDA submission**

NEOPROBE'S RESPONSE:

NEOPROBE HAS DOCUMENTED THE TIME INTERVAL BETWEEN TECHNETIUM Tc 99m LYMPHOSEEK[®] INJECTION AND IN VIVO COUNTING WITH THE GAMMA DETECTION PROBE IN TRIALS NEO3-01, NEO3-05, AND NEO3-09.

AS AGREED WITH THE AGENCY, EX VIVO COUNTING OF LYMPH NODES IS NOT A PROSPECTIVE PLANNED FEATURE OF THE PROTOCOLS FOR NEO3-01, NEO3-05 AND NEO3-09.

AS DISCUSSED WITH THE AGENCY IN THE MARCH 2, 2010, THE AGENCY STATED THAT NEOPROBE, "SHOULD REMOVE EX VIVO COUNTING FROM THE NEO3-06 PROTOCOL AS A COMPONENT OF THE VALIDATION OF *HOT* LYMPH NODES".

- d) **Provide in the NDA submission a subgroup analysis comparing efficacy results (e.g. concordance with blue dye, sensitivity, specificity) among patients with different post-injection time intervals (e.g. 15 min – 2hrs, 2 – 6 hrs, 6 – 10 hrs, 10 – 16 hrs, etc)**

NEOPROBE'S RESPONSE:

ALTHOUGH NOT INCLUDED IN THE PROSPECTIVE STATISTICAL ANALYSIS PLAN, THESE DATA COLLECTED IN ALL PHASE 2 AND PHASE 3 STUDIES INCLUDES THESE OBSERVATIONS. NEOPROBE WILL CONDUCT THE AGENCY'S REQUESTED ADDITIONAL RETROSPECTIVE EXPLORATORY ANALYSES ON THE SUBGROUPS AND INCLUDE THESE IN THE NDA SUBMISSION.

DISCUSSION:

FDA requested an update of the NEO3-09 enrollment. The sponsor concurred.

ACTION ITEMS:

- The sponsor to submit the final analysis and data of the NEO3-09 in the initial NDA submission.

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

/s/

SHARON P THOMAS
10/13/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 61, 757

Neoprobe Corporation
Attention: Rodger Brown
V.P., Regulatory Affairs and Quality Assurance
425 Metro Place North, Suite 300
Dublin, Ohio 43017-1367

Dear Mr. Brown:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Lymphoseek®.

We also refer to the meeting between representatives of your firm and the FDA on October 24, 2007. The purpose of the meeting was to discuss and obtain consensus on the design of two pivotal Phase 3 clinical studies that will be used to support a New Drug Application (NDA) for marketing approval of Lymphoseek®.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1972.

Sincerely,

{See appended electronic signature page}

Tiffany Brown, M.P.H.
Regulatory Health Project Manager
Division of Medical Imaging and
Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

MEMORANDUM OF MEETING MINUTES

APPLICATION: IND 61, 757

DRUG: Lymphoseek®

DATE: October 24, 2007

BETWEEN:

Name: Dave Bupp, President/CEO
Rodger Brown, RAC, VP, RA/QA
Richard Orahoad, M.D., Medical Director
 (b) (4)

Representing: Neoprobe Corporation

AND

Name: Rafel Dwaine Rieves, MD, Acting Division Director
Louis Marzella, M.D., Ph.D., Acting Deputy Director
Cynthia Welsh, M.D., Clinical Reviewer
Jyoti, Zalkikar, Ph.D., Statistical Team Leader, OB
Richard Chen, Ph.D., Statistical Reviewer, OB
Young Moon Choi, Ph.D., Clinical Pharmacology Team Leader
Christy John, Ph.D., Clinical Pharmacologist
Eldon Leutzinger, Ph.D., Chemist, ONDQA
Stephen Langille, Ph.D., Microbiologist, OPS
Kyong Kaye Kang, Pharm.D., Chief, Project Management Staff
Tiffany Brown, Regulatory Health Project Manager

Representing: The Division of Medical Imaging and Hematology Products

DISCUSSION: Please note that the information in **bold** reflects discussion points between FDA and the Sponsor during the Face-to-Face Meeting/Teleconference. Items that are not in bold reflect Division comments and or requests for information from the Sponsor prior to the teleconference. The Division of Medical Imaging and Hematology Products submitted comments to the Sponsor on October 23, 2007. Those comments are provided below for reference. *Please refer to the Appendix to note the Sponsor's unofficial responses to the FDA information requests that were sent prior to the meeting.*

I. Chemistry, Manufacturing and Controls (firm notified on October 19, 2007):

Please provide a package insert and a certificate of analysis (COA) [REDACTED] (b) (4)

FDA/Sponsor Discussion: The Sponsor submitted a package insert; summary of product characteristics; and a certificate of analysis to the FDA on October 23, 2007.

The FDA deemed this information to be acceptable. The Sponsor further informed FDA that the Sponsor intends to use the [REDACTED] (b) (4)

II. Microbiology: (See Appendix for Sponsor's unofficial responses)

1. Because the results of sterility testing will be unavailable prior to administration, [REDACTED] (b) (4)

FDA/Sponsor Discussion: The FDA agreed that the Sponsor's response is acceptable. However, the FDA stated that [REDACTED] (b) (4) used to sterilize the drug must be adequate. The Sponsor agreed to provide a formal response to the FDA's inquiry.

2. Sterility and endotoxin testing should be conducted on each batch of the drug product. Current USP chapter <71> and <85> offer acceptable methods for sterility and endotoxin testing respectively. Endotoxin testing (USP<85>) offers a significant advantage over pyrogen testing (USP<151>) because the results are available within minutes. If testing is done according to USP <85>, endotoxin levels in the drug product should be available prior to administration.

FDA/Sponsor Discussion: The FDA informed the Sponsor that all batches of the drug product should be tested prior to administration. Furthermore, the FDA encouraged the Sponsor to use the endotoxin testing (USP <85>), instead of pyrogen testing (USP <151>) in order to obtain the test results prior to administration. The Sponsor agreed to provide the FDA with a complete response to this question.

3. Sterility and endotoxin testing should be conducted on each batch of diluent vials. Acceptable results should be obtained prior to the preparation of the product vials.

FDA/Sponsor Discussion: Same answer as #2.

4. The storage conditions (time, temperature, and location) for the syringes containing the 1ml patient doses should be defined.

FDA/Sponsor Discussion: Sponsor agreed to provide a more detailed response to the FDA in a future submission.

5. The source of sterile vials and stoppers or the method(s) of on-site sterilization should be provided.

FDA/Sponsor Discussion: FDA and Sponsor reached agreement. Sponsor's response is acceptable.

6.  (b) (4)

FDA/Sponsor Discussion: FDA and Sponsor reached agreement. Sponsor's response is acceptable.

III. Clinical and Statistical Comments: *(See Appendix for Sponsor's unofficial responses)*

We refer you to IND 61, 757, Serial No. 022 dated September 21, 2007 and to your protocols:



Linked Applications

Sponsor Name

Drug Name

IND 61757

NEOPROBE CORP

[TC-99M]DTPA-MANNOSYL-DEXTRAN

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

/s/

TIFFANY J BROWN

11/23/2007