CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202207Orig1s000

PROPRIETARY NAME REVIEW(S)

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

Proprietary Name Review--Final

Date:	January 15, 2013
Reviewer:	Kevin Wright, PharmD Division of Medication Error and Prevention Analysis
Team Leader:	Yelena Maslov, PharmD Division of Medication Error and Prevention Analysis
Drug Name and Strength:	Lymphoseek (Kit for Preparation of Technetium Tc 99m Tilmanocept Injection) 250 mcg per vial
Application Type/Number:	NDA 202207
Applicant/sponsor:	Navidea Biopharmaceuticals, Inc.
OSE RCM #:	2012-2766

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

CONTENTS

1 INTRODUCTION

This re-assessment of the proposed proprietary name, Lymphoseek, is written in response to the anticipated approval of this NDA within 90 days from the date of this review. DMEPA found the proposed name, Lymphoseek, acceptable in OSE Reviews 2010-920, 2011-3175, 2011-4483 dated November 12, 2010, November 16, 2010 and August 7, 2012 respectively.

2 METHODS AND DISCUSSION

For re-assessments of proposed proprietary names, DMEPA searches a standard set of databases and information sources (see section 4) to identify names with orthographic and phonetic similarity to the proposed name that have been approved since the previous OSE proprietary name review. For this review we used the same search criteria described in OSE Reviews 2011-4483. We note that none of the proposed product characteristics were altered. However, we evaluated the previously identified names of concern considering any lessons learned from recent post-marketing experience, which may have altered our previous conclusion regarding the acceptability of the proposed proprietary name. The searches of the databases yielded no new names, thought to look or sound similar to Lymphoseek and represent a potential source of drug name confusion.

Additionally, DMEPA searched the USAN stem list to determine if the name contains any USAN stems as of the last USAN updates. The Safety Evaluator did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, as of January 7, 2013. The Office of Prescription Drug Promotion (OPDP) re-reviewed the proposed name on January 11, 2013 and had no concerns regarding the proposed name from a promotional perspective.

3 CONCLUSIONS

The re-evaluation of the proposed proprietary name, Lymphoseek, did not identify any vulnerabilities that would result in medication errors with any additional name(s) noted in this review. Thus, DMEPA has no objection to the proprietary name, Lymphoseek, for this product at this time.

DMEPA considers this a final review; however, if approval of the NDA is delayed beyond 90 days from the date of this review, the Division of Medical Imaging Products should notify DMEPA because the proprietary name must be re-reviewed prior to the new approval date.

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

4 REFERENCES

1. OSE Reviews

Abdus-Samad, Jibril. OSE Review 2011-4483: Proprietary Name Review for Lymphoseek, August 7, 2012

Abdus-Samad, Jibril. OSE Review 2011-3175: Proprietary Name Review for Lymphoseek, November 16, 2011

Park, Judy. OSE Review 2010-920: Proprietary Name Review for Lymphoseek, November 12, 2010

2. Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and "Chemical Type 6" approvals.

3. USAN Stems (http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/approved-stems.page?)

USAN Stems List contains all the recognized USAN stems.

4. Division of Medication Error Prevention and Analysis Proprietary Name Consultation Request

Compiled list of proposed proprietary names submitted to the Division of Medication Error Prevention and Analysis for review. The list is generated on a weekly basis from the Access database/tracking system.

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/s/

KEVIN WRIGHT
01/15/2013

YELENA L MASLOV
01/15/2013

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

Proprietary Name Review--Final

Date:	August 7, 2012
Reviewer:	Jibril Abdus-Samad, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Todd Bridges, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Lymphoseek (Kit for the Preparation of Technetium Tc 99m Tilmanocept Injection) 250 mcg/vial
Application Type/Number:	NDA 202207
Applicant:	Navidea Biopharmaceuticals, Inc.
OSE RCM #:	2011-4483

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CONTENTS

1 INTRODUCTION

This re-assessment of the proposed proprietary name, Lymphoseek, is written in response to the anticipated approval of this NDA within 90 days from the date of this review. DMEPA found the proposed name, Lymphoseek, acceptable in OSE Reviews 2010-920 and 2011-3175 dated November 12, 2010 and November 16, 2011, respectively.

2 METHODS AND DISCUSSION

For re-assessments of proposed proprietary names, DMEPA searches a standard set of databases and information sources (see section 4) to identify names with orthographic and phonetic similarity to the proposed name that have been approved since the previous OSE proprietary name review. For this review, we used the same search criteria described in OSE Review 2011-3175. We note that none of the proposed product characteristics were altered. However, we evaluated the previously identified names of concern considering any lessons learned from recent post-marketing experience, which may have altered our previous conclusion regarding the acceptability of the proposed proprietary name. The searches of the databases yielded no new names thought to look or sound similar to Lymphoseek and represent a potential source of drug name confusion.

Additionally, DMEPA searched the USAN stem list to determine if the name contains any USAN stems as of the last USAN updates. The Safety Evaluator did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, as of August 6, 2012. The Office of Prescription Drug Promotion re-reviewed the proposed name on March 8, 2012, and had no concerns regarding the proposed name from a promotional perspective.

3 CONCLUSIONS

The re-evaluation of the proposed proprietary name, Lymphoseek, did not identify any vulnerability that would result in medication errors. Thus, DMEPA has no objection to the proprietary name, Lymphoseek, for this product at this time.

DMEPA considers this a final review; however, if approval of the NDA is delayed beyond 90 days from the date of this review, the Division of Medical Imaging Products should notify DMEPA because the proprietary name must be re-reviewed prior to the new approval date.

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

4 REFERENCES

1. OSE Reviews

Park, Judy. OSE Review 2010-920: Proprietary Name Review for Lymphoseek, November 12, 2010

Abdus-Samad, Jibril. OSE Review 2011-3175: Proprietary Name Review for Lymphoseek, November 16, 2011

2. Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and "Chemical Type 6" approvals.

3. USAN Stems (http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/approved-stems.page?)

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/s/

JIBRIL ABDUS-SAMAD
08/07/2012

TODD D BRIDGES
08/07/2012

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

Proprietary Name Review

Date:	November 16, 2011
Reviewer:	Jibril Abdus-Samad, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Todd Bridges, RPh Division of Medication Error Prevention and Analysis
Division Director:	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Lymphoseek (Kit for the Preparation of Technetium Tc 99m Tilmanocept for Injection) 0.25 mg/vial
Application Type/Number:	NDA 202207
Applicant:	Neoprobe Corporation
OSE RCM #:	2011-3175

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CONTENTS

1 INTRODUCTION

This review evaluates the proposed proprietary name, Lymphoseek, from a safety and promotional perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A respectively.

1.1 REGULATORY HISTORY

The proposed proprietary name, Lymphoseek, was found acceptable in OSE Review 2010-920, dated November 12, 2010 during the IND phase. The product characteristics of Lymphoseek remain the same for this submission.

1.2 PRODUCT INFORMATION

The following product information is provided in the August 22, 2011 proprietary name submission.

- Established Name: (b) (4)
- Indication of Use: (b) (4)
- Route of administration: intradermal, subcutaneous, subareolar, or peritumoral injection
- Dosage form: For Injection
- Dose: 50 mcg Lymphoseek radiolabeled with Technetium Tc 99m at 18.5 MBq (0.5 mCi) for same day surgery (b) (4)
- How Supplied: Lymphoseek®: Kit for the Preparation of Technetium Tc 99m Tilmanocept for Injection includes five (5) Lymphoseek vials containing 0.25 mg tilmanocept per vial and five (5) vials of sterile buffered saline diluent containing 4.5 mL per vial. Each kit also includes prescribing information, (b) (4), and five (5) radioassay information labels.
- Storage: Store at (b) (4) before and after reconstitution. Store reconstituted product using appropriate radiation shielding. The expiration date and time are provided on the radioassay information label. Use within 6 hours after reconstitution.
- Container and Closure systems: 5 mL glass tubing vials with a (b) (4) stopper and (b) (4) seals for Lymphoseek (Tilmanocept) and 4.5 mL vial for diluent

2 RESULTS

The following sections provide the information obtained and considered in the evaluation of the proposed proprietary name.

2.1 PROMOTIONAL ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined the proposed name is acceptable from a promotional perspective. DMEPA and the Division of Medical Imaging Products (DMIP) concurred with the findings of OPDP's promotional assessment of the proposed name.

2.2 SAFETY ASSESSMENT

The following aspects of the name were considered in the overall evaluation.

2.2.1 United States Adopted Names (USAN) SEARCH

On November 6, 2011 the United States Adopted Name (USAN) stem search identified that a USAN stem is not present in the proposed proprietary name.

2.2.2 Components of the Proposed Proprietary Name

This proprietary name comprised of a single word that does not contain any components such as a modifier, route of administration, dosage form, or a medical abbreviation that is misleading or can contribute to medication error. However, the proposed proprietary name, Lymphoseek, does suggest its proposed indication for use in the (b) (4) localization of lymph nodes or simply put *seek lymph*. This may not be error prone if and when Lymphoseek is initially approved by itself; however, suggestion of the indication may lead to confusion if the Applicant pursues additional indications unrelated to (b) (4) of lymph nodes.

2.2.3 FDA Name Simulation Studies

Thirty-one practitioners participated in DMEPA's prescription studies. The interpretations did not overlap with, appear, or sound similar to any currently marketed products. The most common misinterpretation in the Outpatient Study was the lowercase letter 'h' for capital letter 'L'. See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

2.2.4 Comments from Other Review Disciplines

In response to the OSE, September 1, 2011 e-mail, the DMIP did not forward any comments or concerns relating to the proposed name at the initial phase of the proprietary name review.

2.2.5 Failure Mode and Effects Analysis of Similar Names

Appendix B lists possible orthographic and phonetic misinterpretations of the letters appearing in the proposed proprietary name, Lymphoseek. Table 1 lists the names with orthographic, phonetic, or spelling similarity to the proposed proprietary name, Lymphoseek, identified by the primary reviewer, the Expert Panel Discussion (EPD), and other review disciplines. Additionally, any names identified that were previously

evaluated in OSE Review 2010-920 that had no changes in product characteristics are listed in Appendix D.

Table 1: Collective List of Potentially Similar Names (DMEPA, EPD, Other Disciplines, FDA Name Simulation Studies, and External Name Study if applicable)

Look Similar		**Sound Similar**		**Look and Sound Similar**	
Name	***Source***	***Name***	***Source***	***Name***	***Source***
Cyclocort	FDA	Lincocin	FDA	Lymphazurin	FDA
Cycloset	FDA			Lymphoscan	FDA
Limbitrol DS	FDA			Lymphocide	FDA
Lincomycin	FDA			Lymphoseek***	FDA
Lumizyme	FDA				
Lycopene	FDA				
Lycopodium	FDA				
Lymecycline	FDA				
Lymphogram	FDA				
Lymphomyosot	FDA				
Lypholyte	FDA				
SyringeAvitene	FDA				
Lymphocyte Immune Globulin	FDA				
Lymphocyte Mitogenic Factor	FDA				
Tympagesic	FDA				

(b) (4)	FDA				
Hyphanox***	FDA				

Our analysis of the 22 names contained in Table 1 considered the information obtained in the previous sections along with their product characteristics. We determined the 22 names will not pose a risk for confusion as described in Appendix D through F.

2.2.6 Communication of DMEPA's Final Decision to Other Disciplines

DMEPA communicated our findings to the DMIP via e-mail on November 10, 2011. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the DMIP on November 15, 2011, they stated no additional issues with the proposed proprietary name, Lymphoseek.

3 CONCLUSIONS

The proposed proprietary name is acceptable from both a promotional and safety perspective.

The proposed proprietary name, Lymphoseek, must be re-reviewed 90 days before approval of the NDA.

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

3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Lymphoseek, and have concluded that this name is acceptable. However, if any of the proposed product characteristics as stated in your August 22, 2011 submission are altered, DMEPA rescinds this finding and the name must be resubmitted for review. Additionally, this proprietary name must be re-evaluated 90 days prior to the approval of the application. The conclusions upon re-review are subject to change.

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4 REFERENCES

1. ***Micromedex Integrated Index (http://csi.micromedex.com)***

   Micromedex contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

2. ***Phonetic and Orthographic Computer Analysis (POCA)***

   POCA is a database which was created for the Division of Medication Error Prevention and Analysis, FDA. As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion.

3. ***Drug Facts and Comparisons, online version, St. Louis, MO (http://factsandcomparisons.com)***

   Drug Facts and Comparisons is a compendium organized by therapeutic course; it contains monographs on prescription and OTC drugs, with charts comparing similar products. This database also lists the orphan drugs.

4. ***FDA Document Archiving, Reporting & Regulatory Tracking System [DARRTS]***

   DARRTS is a government database used to organize Applicant and Sponsor submissions as well as to store and organize assignments, reviews, and communications from the review divisions.

5. ***Division of Medication Errors Prevention and Analysis proprietary name consultation requests***

   This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

6. ***Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)***

   Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and "Chemical Type 6" approvals.

7. ***U.S. Patent and Trademark Office (***http://www.uspto.gov***)***

   USPTO provides information regarding patent and trademarks.

8. ***Clinical Pharmacology Online (www.clinicalpharmacology-ip.com)***

   Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common,

combination, nutraceutical and nutritional products. It also provides a keyword search engine.

9. ***Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at (www.thomson-thomson.com)***

   The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

10. ***Natural Medicines Comprehensive Databases (www.naturaldatabase.com)***

    Natural Medicines contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

11. ***Access Medicine*** *(www.accessmedicine.com)*

    Access Medicine® from McGraw-Hill contains full-text information from approximately 60 titles; it includes tables and references. Among the titles are: Harrison's Principles of Internal Medicine, Basic & Clinical Pharmacology, and Goodman and Gilman's The Pharmacologic Basis of Therapeutics.

12. ***USAN Stems (http://www.ama-assn.org/ama/pub/about-ama/our-people/coalitions-consortiums/united-states-adopted-names-council/naming-guidelines/approved-stems.shtml)***

    USAN Stems List contains all the recognized USAN stems.

13. ***Red Book Pharmacy's Fundamental Reference***

    Red Book contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

14. ***Lexi-Comp (www.lexi.com)***

    Lexi-Comp is a web-based searchable version of the Drug Information Handbook.

15. ***Medical Abbreviations Book***

    Medical Abbreviations Book contains commonly used medical abbreviations and their definitions.

16. ***CVS/Pharmacy (www.CVS.com)***

    This database contains commonly used over the counter products not usually identified in other databases.

17. ***Walgreens (www.walgreens.com)***

    This database contains commonly used over the counter products not usually identified in other databases.

18. Rx List (www.rxlist.com)

RxList is an online medical resource dedicated to offering detailed and current pharmaceutical information on brand and generic drugs.

19. Dogpile (www.dogpile.com)

Dogpile is a Metasearch engine that searches multiple search engines including Google, Yahoo! and Bing, and returns the most relevant results to the search.

20. OSE Review

Park, Judy. OSE Review 2010-920: Proprietary Name Review for Lymphoseek, November 12, 2010.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment considers the promotional and safety aspects of a proposed proprietary name. The promotional review of the proposed name is conducted by OPDP. OPDP evaluates proposed proprietary names to determine if they are overly fanciful, so as to misleadingly imply unique effectiveness or composition, as well as to assess whether they contribute to overstatement of product efficacy, minimization of risk, broadening of product indications, or making of unsubstantiated superiority claims. OPDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.

The safety assessment is conducted by DMEPA. DMEPA staff search a standard set of databases and information sources to identify names that are similar in pronunciation, spelling, and orthographically similar when scripted to the proposed proprietary name. Additionally, we consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.). DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

Following the preliminary screening of the proposed proprietary name, DMEPA gathers to discuss their professional opinions on the safety of the proposed proprietary name. This meeting is commonly referred to the Center for Drug Evaluation and Research (CDER) Expert Panel discussion. DMEPA also considers other aspects of the name that may be misleading from a safety perspective. DMEPA staff conducts a prescription simulation studies using FDA health care professionals. When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name and misleading nature of the proposed proprietary name with a focus on the avoidance of medication errors.

DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product. DMEPA considers the product characteristics associated with the proposed product throughout the risk assessment because the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

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[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. DMEPA considers how these product characteristics may or may not be present in communicating a product name throughout the medication use system. Because drug name confusion can occur at any point in the medication use process, DMEPA considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.[2] The product characteristics considered for this review appears in Appendix B1 of this review.

The DMEPA considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA compares the proposed proprietary name with the proprietary and established name of existing and proposed drug products and names currently under review at the FDA. DMEPA compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. DMEPA examines the phonetic similarity using patterns of speech. If provided, DMEPA will consider the Sponsor's intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Sponsor has little control over how the name will be spoken in clinical practice. The orthographic appearance of the proposed name is evaluated using a number of different handwriting samples. DMEPA applies expertise gained from root-cause analysis of postmarketing medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g.,"T" may look like "F," lower case 'a' looks like a lower case 'u,' etc). Additionally, other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details).

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

Table 1. Criteria Used to Identify Drug Names that Look- or Sound-Similar to a Proposed Proprietary Name.

Type of Similarity	**Considerations when Searching the Databases**		
	Potential Causes of Drug Name Similarity	*Attributes Examined to Identify Similar Drug Names*	*Potential Effects*
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	• Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication • Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name/Similar shape Upstrokes Down strokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	• Names may look similar when scripted, and lead to drug name confusion in written communication
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Lastly, DMEPA considers the potential for the proposed proprietary name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. Consequently, DMEPA considers and evaluates these broader safety implications of the name throughout this assessment and the medication error staff provides additional comments related to the

safety of the proposed proprietary name or product based on professional experience with medication errors.

1. Database and Information Sources

DMEPA searches the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to the proposed proprietary name. A standard description of the databases used in the searches is provided in the reference section of this review. To complement the process, the DMEPA uses a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, DMEPA reviews the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel. DMEPA also evaluates if there are characteristics included in the composition that may render the name unacceptable from a safety perspective (abbreviation, dosing interval, etc.).

2. Expert Panel Discussion

DMEPA gathers gather CDER professional opinions on the safety of the proposed product and discussed the proposed proprietary name (Expert Panel Discussion). The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Division of Drug Marketing, Advertising, and Communications (OPDP). We also consider input from other review disciplines (OND, ONDQA/OBP). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

The primary Safety Evaluator presents the pooled results of the database and information searches to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend additional names, additional searches by the primary Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

3. FDA Prescription Simulation Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically

scanned and one prescription is delivered to a random sample of participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants record their interpretations of the orders which are recorded electronically.

4. Comments from Other Review Disciplines

DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

5. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, considers all aspects of the name that may be misleading or confusing, conducts a Failure Mode and Effects Analysis, and provides an overall decision on acceptability dependent on their risk assessment of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.[3] When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product

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

characteristics listed in Appendix B1 of this review. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, Expert Panel Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

> ***"Is the proposed proprietary name convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting? And Are there any components of the name that may function as a source of error beyond sound/look-alike"***

An affirmative answer indicates a failure mode and represents a potential for the proposed proprietary name to be confused with another proprietary or established drug name because of look- or sound-alike similarity or because of some other component of the name. If the answer to the question is no, the Safety Evaluator is not convinced that the names posses similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes to determine the likely *effect* of the drug name confusion, by asking:

> ***"Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?"***

The answer to this question is a central component of the Safety Evaluator's overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend the use of an alternate proprietary name.

Moreover, DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the Overall Risk Assessment:

a. OPDP finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with OPDP's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].

b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].

c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.

d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.

e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product but involve a naming characteristic that when incorporated into a proprietary name, may be confusing, misleading, cause or contribute to medication errors.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA generally recommends that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

The threshold set for objection to the proposed proprietary name may seem low to the Applicant/Sponsor. However, the safety concerns set forth in criteria a through e above are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), the Joint Commission, and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names, confusing, or misleading names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, the Agency and/or Sponsor can identify and rectify prior to approval to avoid patient harm.

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Sponsors have undertaken higher-leverage strategies, such as drug name changes, in the

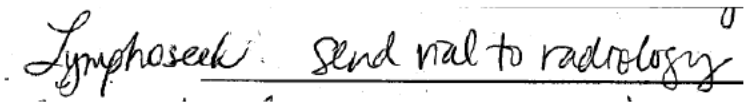
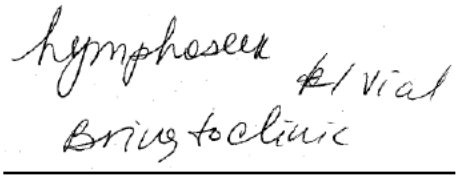
past but at great financial cost to the Sponsor and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Sponsors' have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval.

Appendix B: Letters with Possible Orthographic or Phonetic Misinterpretation

Letters in Name, Lymphoseek	Scripted May Appear as	Spoken May Be Interpreted as
capital letter 'L'	C, F, h, I, S, T, Z	
lowercase 'l'	A, b,e, i, s, P,	
lowercase 'y'	f, g, p, u, v, x, Z	e, i, u
lowercase 'm'	nn, n, rn, onc, u, v, w, wi, vi, z	n
lowercase 'p'	g, j, l, q, yn, ys,	
lowercase 'h'	b, k, L ,n	
lowercase 'ph'		f
lowercase 'o'	a, c, e, u	a, u
lowercase 's'	G, 5, g, n,	ce, x, z
lowercase 'e'	a, i, l, o, u, p	a, i
lowercase 'k'	x, h, la	c, g

Appendix C: Prescription Simulation Samples and Results

Figure 1. Lymphoseek Study (Conducted on September 19, 2011)

Handwritten Medication Order	Verbal Prescription
Medication Order:  	Lymphoseek Dispense 1 vial
Outpatient Prescription:  	

FDA Prescription Simulation Responses.

Inpatient Medication Order	Outpatient Prescription	Voice Prescription
Lymphoseek	Lemphoseek	Hymphasun
Lymphoseek	Lymphocic	Hymphoseel
Lymphoseek	Lymphocit	Hymphoseen
Lymphoseek	Lymphoseek	Hymphoseic
Lymphoseek	Lymphoseek	Hymphoseu
Lymphoseek	Lymphoseek	Hymphoslu
Lymphoseek	Lymphoseek	Lymphasun
Lyphoseek	Lymphoseek	Lymphosect
	Lymphosic	Lymphoseek
		Lymphoseek
		Lymphoseek
		Lymphoseek
		Lymphoseer
		Lymphosex

Appendix D: Proprietary names determined in OSE Review 2010-920 not likely to lead to a medication error.

Proprietary Name	Active Ingredient	Similarity to Lymphoseek
Cycloset	Bromocriptine Mesylate	Look
Lymphocyte Immune Globulin (Proprietary name: Atgam)	Antithymocyte Globulin	Look
Tympagesic	Antipyrine, Benzocaine, Phenylephrine Hydrochloride	Look
Lymphazurin	Isosulfan Blue	Look / Sound
Lymphoscan	Technetium Tc 99m Murine Monoclonal Antibody to B cell	Look / Sound
Lymphocide	Epratuzumab	Look / Sound

Appendix E: Proprietary names not likely to be confused or not used in usual practice settings for the reasons described.

Proprietary Name	Active Ingredient	Similarity to Lymphoseek	Failure preventions
Limbitrol DS	Amitriptyline and Chlordiazepoxide	Look	Lacks significant orthographic similarity
	Lincomycin	Look	Lacks significant orthographic similarity
Lumizyme	Alglucosidase alpha	Look	Lacks significant orthographic similarity
	Lycopodium	Look	No product characteristics available in drug information databases
SyringeAvitene	Microfibrillar product, Bovine derived	Look	Lacks significant orthographic similarity
Hyphanox***	Itraconazole	Look	DMEPA denied name in OSE Review 2009-1204. NDA approved with proprietary name, *Onmel*, 4/28/2010
	Lymecycline	Look	Foreign product, not approved in US
Lymphogram		Look	Identified in Micromedex database; however no product characteristics available in other databases listed in Section 4 - References.
Lincocin	Lincomycin	Sound	Lacks significant phonetic similarity
Lymphoseek***	Technetium Tc 99m Tilmanocept	Look and Sound	Trademark of Neoprobe, which is the Applicant for this NDA

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Appendix F: Risk of medication errors due to product confusion minimized by dissimilarity of the names and/ or use in clinical practice for the reasons described.

Proposed name: **Lymphoseek**	**Strength:** **0.25 mg Tilmanocept per vial**	**Usual dose:** **50 mcg dose injection, radiolabeled with 0.5 mCi to 2 mCi Technetium Tc 99m**
Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion	**Causes (could be multiple)**	**Prevention of Failure Mode**
Cyclocort (Amcinonide) 0.1% Topical Cream, Lotion, and Ointment Usual Dose: Apply sparingly to the affected area two to three times daily.	**Orthographic similarity** – Both names have upstroke letters ('C' vs. 'L', 'l' vs. 'h', 't' vs. 'k') and downstroke letters ('y') in similar positions	**Orthographic differences** - Middle portion of the names differ (-clocor- vs. -mphosee-) and Lymphoseek contains an additional downstroke letter 'p' in the near the middle of the name. - Lymphoseek appears longer than Cyclocort **Context of use** - Radiopharmaceutical procurement, prescribing, transcription, preparation, and administration is significantly separated from traditional pharmacy.
Lycopene Strength: 10 mg, 15 mg, 30 mg tablets or capsules Usual Dose: Take 1 tablet or capsule daily	**Orthographic similarity** - The beginning of both names appear similar when scripted (Lycop- vs. Lymp-)	**Orthographic differences** - the ending of the names differ (-ene vs. -hoseek) **Product characteristic differences** - Dose: 10 mg, 15 mg, 30 mg vs. 0.5 mCi to 2 mCi **Context of use** - Radiopharmaceutical procurement, prescribing, transcription, preparation, and administration is significantly separated from traditional pharmacy.

Proposed name: **Lymphoseek**	**Strength:** **0.25 mg Tilmanocept per vial**	**Usual dose:** **50 mcg dose injection, radiolabeled with 0.5 mCi to 2 mCi Technetium Tc 99m**
Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion	**Causes (could be multiple)**	**Prevention of Failure Mode**
Lymphomyosot (Geranium Robertianum, Rorippa Nasturtium-Aquaticum, Sarsaparilla Root, Tribasic Calcium Phosphate, and Levothyroxine) Injection Solution Dose: 1 ampule per day or 3 to 5 times per week intramuscularly, subcutaneously, intravenously, or intradermally. Oral Solution 50 mL Dose: 10 drops orally 3 times daily	**Orthographic similarity** - Both name have identical beginning letters (Lympho-), both names end with an upstroke letter ('t' vs. 'k')	**Orthographic differences** - the ending of the names differ (-myosot vs. -seek), mainly due to the additional downstroke letter 'y' in Lymphomyosot. **Product characteristic differences** - Dose: 10 drops or 1 ampule vs. 0.5 mCi to 2 mCi **Context of use** - Radiopharmaceutical procurement, prescribing, transcription, preparation, and administration is significantly separated from homeopathic products. - Preliminary Drug Use search retrieved no data of Lymphomyosot (homeopathic medication) by outpatient physicians.
Lypholyte (Acetate, Calcium, Chloride, Gluconate, Magnesium, Potassium, Sodium) Multi-Electrolyte Concentrate Solution for Injection (6 mEq/5 mEq/ 33.5 mEq/5 mEq/ 8 mEq/ 40.5 mEq/ 25 mEq per 20 mL) Usual Dose: Dilute prior to administration based on individual needs (20 mL to 25 mL)	**Orthographic similarity** - Both names share identical letters in the beginning of the names ('Ly', 'pho')	**Orthographic differences** - the endings of the names differ ('-lyte' vs. '-seek') **Product characteristic differences** - Dose: 20 mL to 25 mL vs. vs. 0.5 mCi to 2 mCi - Lypholyte will appear on a total parenteral nutrition order and not ordered or administered separately. **Context of use** - Radiopharmaceutical procurement, prescribing, transcription, preparation, and administration is significantly separated from traditional pharmacy

Proposed name: Lymphoseek	Strength: 0.25 mg Tilmanocept per vial	Usual dose: 50 mcg dose injection, radiolabeled with 0.5 mCi to 2 mCi Technetium Tc 99m
Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion	**Causes (could be multiple)**	**Prevention of Failure Mode**
Lymphocyte Mitogenic Factor Proleukin (Aldesleukin) 22 million International Units (1.3 mg) for injection Usual Dose: 600,000 International Units/kg intravenously every 8 hrs for up to 14 doses 18 million International Units/m^2/day intravenously for two 5 day cycles 1800 International Units/m^2 up to 18 million International Units/m^2 daily subcutaneously for 5 days	**Orthographic similarity** - Both share identical beginning (Lympho-')	**Orthographic differences** - the endings of the names differ ('cyte' vs. '-seek'). - the length of the names are significantly different (Lymphocyte Mitogenic Factor Globulin 25 letters vs. Lymphoseek 10 letters) **Product characteristic differences** - Dose: 30 million units to 60 million units vs. vs. 0.5 mCi to 2 mCi - Medication orders are likely to contain the proprietary or established names [Proleukin (Aldesleukin)]. **Context of use** - Radiopharmaceutical procurement, prescribing, transcription, preparation, and administration is significantly separated from traditional pharmacy

Proposed name: Lymphoseek	Strength: 0.25 mg Tilmanocept per vial	Usual dose: 50 mcg dose injection, radiolabeled with 0.5 mCi to 2 mCi Technetium Tc 99m
Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion	**Causes (could be multiple)**	**Prevention of Failure Mode**
[redacted]	[redacted]	[redacted] (b) (4)

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/s/

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