CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202317Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 202317	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Valchlor Established/Proper Name: mechlorethamine Dosage Form: gel Strengths: 0.016%		
Applicant: Ceptaris Therapeutics Inc. (formerly Yaupon Therapeutics Inc.)		
Date of Receipt: 2/27/13		
PDUFA Goal Date: 8/27/13	Action Goal Date (if different): 8/23/13	
RPM: Tyree Newman		
Proposed Indication(s): Treatment of Stage IA and IB mycosis fungoides-type cutaneous T-cell lymphoma in patients who have received prior skin-directed therapy		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Reference ID: 3361834

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Mustargen	NDA 6695 (for nonclinical sections of the label)
Literature	Nonclinical toxicology of an excipient Nonclinical studies of the active pharmaceutical ingredient

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

There is a scientific bridge as the active pharmaceutical ingredient (API) of Valchlor is identical to that of Mustargen. Also, the Applicant conducted a clinical trial that demonstrated a relationship between the referenced and proposed products which was deemed acceptable by the clinical review team.. Nonclinical findings described in the label for Mustargen as related to the API may be used for nonclinical sections of Valchlor label. In addition, articles describing toxicities of the API in nonclinical studies may be used to label the nonclinical sections of Valchlor.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

Reference ID: 3361834

YES ☒ NO ☐

*If "**NO**", proceed to question #5.*
*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

Mustargen®

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☒ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Mustargen®	NDA 6695	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*
*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:
   a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Reference ID: 3361834

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a new route of administration (topical) and a new formulation for the approved indication of mycosis fungoides.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled*

Reference ID: 3361834

syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; ***(2)*** *do not necessarily contain the same inactive ingredients;* ***and*** ***(3)*** *meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

Note *that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

If this application relies only on non product-specific published literature, answer ***"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

Note *that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

Reference ID: 3361834

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note *that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information* ***UNLESS*** *the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

Reference ID: 3361834

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/s/

TYREE L NEWMAN
08/23/2013

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

Label, Labeling and Packaging Memorandum

Date:	July 22, 2013
Reviewer:	Kevin Wright, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Yelena Maslov, PharmD Division of Medication Error Prevention and Analysis
Associate Director:	Scott Dallas, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Valchlor (Mechlorethamine) Gel 0.016%
Application Type/Number:	NDA 202317
Applicant/sponsor:	Ceptaris Therapeutics Inc.
OSE RCM #:	2013-733

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

Contents

1 INTRODUCTION

1.1 REGULATORY HISTORY

This review evaluates the container labels, carton and insert labeling for Valchlor (Mechlorethamine) Gel under NDA 202317, submitted on February 2, 2013. The Division of Medication Error Prevention and Analysis (DMEPA) previously reviewed the proposed container label, carton and insert labeling in OSE Review 2011-3130, dated February 10, 2012.

1.2 PRODUCT INFORMATION

The following product information is provided in the February 27, 2013 submission.

- Intended pronunciation: val´klor
- Active Ingredient: Mechlorethamine
- Indication of Use: treatment of mycosis fungoides
- Route of Administration: Topical
- Dosage Form: Gel
- Strength: 0.016%
- Dose and Frequency: Apply to affected lesions once daily
- How Supplied: 60 gram tube
- Storage: store in freezer at -25°C to -15°C (-13°F to 5°F) before dispensing, after dispensing store in refrigerator at 2°C to 8°C (36°F to 46°F)
- Container and Closure Systems: 60 gram tube in carton

2 METHODS AND MATERIALS REVIEWED

2.1 LABELS AND LABELING

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

- Container Labels submitted February 27, 2013 (Appendix A)
- Carton Labeling submitted February 27, 2013 (Appendix B)
- Insert Labeling submitted May 24, 2013 (no image)

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

Reference ID: 3344710

2.2 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed the container labels, carton and insert labeling in OSE Review# 2011-3130 and we evaluated the review to ensure all our recommendation were implemented.

3 CONCLUSIONS AND RECOMMENDATIONS

The container labels, carton and insert labeling implemented some of the recommendations outlined in the letter to the Applicant on June 11, 2011. However, there are outstanding recommendations along with some newly identified issues. DMEPA provides the following comments for consideration by the review division prior to the approval of this NDA.

I. Comments to the Division

A. Insert Labeling and Medication Guide

1. The route of administration is inconsistently expressed across the products labels and labeling. For example: In the (b) (4) Highlights of Prescribing Information and Full Prescribing Information under the Dosage and Administration section, it states "For Topical Dermatological Use Only"; (b) (4) It is important to be consistent with the presentation of the route of administration throughout the label and labeling to help prevent confusion leading to wrong route of administration errors. Therefore, please ensure the route of administration is consistently presented throughout the labels and labeling. We recommend using the route of administration statement, "For Topical Use".

II. Comments to the Applicant

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

A. Comments for both Container Label & Carton Labeling

1. Revise the proprietary name, Valchlor, to appear in title case (e.g. Valchlor).
2. Ensure the active ingredient and dosage formulation appears at ½ the font size as of the proprietary name taking into account all pertinent factors, including font size, typography, layout, contrast, coloring and other printing features.
3. Decrease the prominence (b) (4) on the container label (b) (4)

Reference ID: 3344710

4. [redacted] (b) (4)
5. Currently, the dosage form "gel" is presented in a different font color, style, and font size than the active ingredient. Revise the dosage form to be presented in the same font size, color as the active ingredient.
6. Revise the route of administration statement to read "For Topical Use". Increase the prominence of the route of administration statement by using different font size and/or color and relocating the statements to appear with a white background, possibly closer to the center of the principal display panel.

B. Container Label

1. Ensure the lot number and expiration date is clearly noted on the container as per 21 CFR 211.130(c) and 21 CFR 201.17.
2. Reduce the font size and unbold the "Rx Only" statement to decrease its prominence and avoid competing with other important information.

C. Carton Labeling

1. Relocate the reference regarding the Medication Guide from the side panel to the principal display panel to increase its prominence.
2. We recommend addition of the following storage statement to the principal display panel (pdp) to inform health care professionals and patients on the proper storage:

Before dispensing, store in Freezer
After dispensing, store Refrigerated

3. Since the storage conditions of this product are different prior to dispensing and after dispensing, please add the following statement to the side display panel of the carton labeling. "Before dispensing freeze at-13°F to 5°F (-25°C to 15C). After dispensing store refrigerated 36°F to 46°F (2°C to 8°C).

If you have further questions or need clarifications, please contact Sue Kang, project manager, at 301-796-4216.

APPENDICES

Appendix A: Container Label

Appendix B: Carton Labeling

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/s/

KEVIN WRIGHT
07/22/2013

YELENA L MASLOV
07/22/2013

SCOTT M DALLAS
07/22/2013

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

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

Memorandum

Date: June 25, 2013

To: Tyree Newman – Regulatory Project Manager
Division of Hematology Products (DHP)

From: Richard Lyght, Pharm.D. – Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP comments on draft Valchlor (mechlorethamine) 0.02% Prescribing Information (PI)

This consult is in response to DHP's March 19, 2013 request for OPDP review of the draft Valchlor Prescribing Information. OPDP comments are based on the proposed draft marked-up labeling revised by the review division and received by OPDP on June 14, 2013.

We have made no comments at this time.

We also note that our comments on the draft Medication Guide were provided in conjunction with DMPP on June 21, 2013

OPDP appreciates the opportunity to provide comments. If you have any questions, please contact Richard Lyght at 301-796-2874 or at richard.lyght@fda.hhs.gov.

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/s/

RICHARD A LYGHT
06/25/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Enhanced Pharmacovigilance Plan for PMC

Date:	June 25, 2013
Reviewer:	Afrouz Nayernama, PharmD, Safety Evaluator, Division of Pharmacovigilance II
Team Leader:	Tracy Salaam, PharmD, Team Leader Division of Pharmacovigilance II
Division Director:	Min Chu Chen, R. Ph., M.S., (Acting) Division of Pharmacovigilance
Product Name:	Valchlor (mechlorethamine) Gel for Topical Use
Subject:	Secondary Exposure
Application Type/Number:	NDA 202317
Applicant/Sponsor:	Ceptaris Therapeutics, Inc.
OSE RCM #:	2013-1470

TABLE OF CONTENTS

1 INTRODUCTION

As part of a prospective roadmap for pharmacovigilance activities during a product's life cycle safety management, beginning with the early postmarketing period, the Division of Pharmacovigilance provides an enhanced pharmacovigilance plan for the 505(b)(2) application for NDA 202317 Valchlor, a proposed trade name for topical mechlorethamine.

1.1 BACKGROUND

Valchlor (mechlorethamine) gel is an alkylating drug indicated for the topical treatment of (b) (4) Stage IA or IB mycosis fungoides type cutaneous T-cell lymphoma who have received at least one prior skin-directed therapy.

The risk of secondary exposure to Valchlor in individuals other than the prescribed patient will be conveyed in the Valchlor product label under Warnings and Precautions. Therefore, after approval, postmarketing reports of secondary exposure will not be required to be submitted as postmarketing 15-day "Alert Reports" as defined under 21 CFR 314.80 (c). The sponsor will submit all secondary exposure events from postmarketing sources in the Periodic Adverse Drug Event (PADER), or the Periodic Benefit-Risk Evaluation Report (PBRER).

1.2 REGULATORY HISTORY

Mechlorethamine has been on the market under the trade name Mustargen since March 15, 1949 for the systemic treatment of various oncological conditions. On July 27, 2011, Ceptaris Therapeutics, Inc. (formerly Yaupon) submitted a 505(b)(2) New Drug Application (NDA) for its proprietary topical formulation containing mechlorethamine. The Prescription Drug User Fee Act (PDUFA) due date is August 27, 2013.

2 POSTMARKETING COMMITMENT (PMC)

2.1 ENHANCED PHARMACOVIGILANCE PLAN FOR SECONDARY EXPOSURE ADVERSE EVENTS

In order to best assess postmarketing reports of secondary exposure, we are requesting that Ceptaris, the sponsor of this topical formulation of mechlorethamine, perform enhanced pharmacovigilance (PV) for a period of up to 2 years after this notification. The primary enhancements to the current routine PV paradigm for these products in this proposal are the following commitments:

- Submit expedited reporting of both serious and non-serious outcomes for all initial and follow-up adverse drug experiences as Postmarketing 15-day "Alert Reports" indicative of secondary exposure in individuals other than the prescribed patient
- Submit a summary, evaluation, and line listing of all secondary exposure events from postmarketing sources, including consumer reports, solicited reports, and foreign reports in the PADER/PBRER.

2.2 DEFINITION OF SECONDARY EXPOSURE

Secondary exposure is defined as an unintentional exposure to Valchlor in individuals other than the prescribed patient, including but not limited to household family members or caregivers.

2.3 REQUESTED DATA

1. The sponsor is expected to perform an active query to obtain the following information for cases defined in Section 2.2 above:
   - exposed individual age, race, and sex (if available)
   - site of exposure i.e. skin, eye, mucosal membrane
   - duration of exposure if applicable
   - time from drug application to exposure
   - time between exposure to mechlorethamine and the onset of the adverse event
   - date of exposure
   - detailed description(s) of adverse events
   - specific laboratory data to confirm the injury and information from definitive surgical procedures, if performed
   - primary treatment(s) for the event
   - patient outcome

2. When postmarketing reports are suggestive, but not confirmatory of adverse events as a result of a secondary exposure, the sponsor is expected to pursue follow-up information to obtain a final diagnosis.

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/s/

AFROUZ R NAYERNAMA
06/25/2013

TRACY M SALAAM
06/25/2013

MIN CHU CHEN
06/25/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	June 21, 2013
To:	Ann Farrell, MD Director **Division of Hematology Products (DHP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Karen Dowdy, RN, BSN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Richard Lyght, Pharm.D. Senior Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	VALCHLOR (mechlorethamine) 0.02%
Dosage Form and Route:	gel, for topical use
Application Type/Number:	NDA 202-317
Applicant:	Ceptaris Therapeutics, Inc.

1 INTRODUCTION

On February 27, 2013, Ceptaris Therapeutics, Inc. re-submitted for the Agency's review original New Drug Application (NDA) 202-317 for VALCHOR (mechlorethamine) Gel, 0.02%. The Division of Hematology Products (DHP) considers the Applicant's submission to be a complete, class 2 response to the Agency's Complete Response Letter, issued on May 4, 2012. The proposed indication for VALCHLOR (mechlorethamine) Gel, 0.02% is for the topical treatment of (b) (4) Stage IA or IB mycosis fungoides type cutaneous T-cell lymphoma who have received at least one prior skin-directed therapy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on March 21, 2013 and March 19, 2013 respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for VALCHLOR (mechlorethamine) Gel 0.02%.

2 MATERIAL REVIEWED

- Draft VALCHLOR (mechlorethamine) MG received on May 24, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 14, 2013.
- Draft VALCHLOR (mechlorethamine) Prescribing Information (PI) received on May 24, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 14, 2013.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 10.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
06/21/2013

BARBARA A FULLER
06/21/2013

LASHAWN M GRIFFITHS
06/21/2013

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

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

Application: NDA 202317

Application Type: New NDA

Name of Drug: Nitrogen Mustard (Mechlorethamine Hydrochloride Gel 0.02%)

Applicant: Ceptaris Therapeutics, Inc.

Submission Date: February 27, 2013

Receipt Date: February 27, 2013

1.0 Regulatory History and Applicant's Main Proposals

Ceptaris provided a resubmission to the Agency's Complete Response Letter (CRL) on February 27, 2013. The CRL was issued on May 4, 2012, and received by Ceptaris on May 7, 2012.

The resubmission contained the following information:

- Release data/characterization of the clinical trial and commercial drug products
- Stability data to support a revised storage condition and expiry for the drug product
- Revised specifications for the drug substance and drug product
- New BHT method validation
- Justification of reliability of previously submitted clinical trial data

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

In addition, the following labeling issues were identified:
All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by May 27, 2013. The resubmitted PI will be used for further labeling review.

Reference ID: 3311645

4.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

YES 4. White space must be present before each major heading in HL.

Comment:

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

Reference ID: 3311645

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*****
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

NO 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

NO 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment: *The statement must be immediately beneath the HL heading.*

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

12. All text must be **bolded**.

Comment:

N/A 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

Comment:

Dosage Forms and Strengths

Reference ID: 3311645

YES 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

N/A 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

NO 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment: *Sponsor must include their telephone number.*

Patient Counseling Information Statement

YES 26. Must include <u>one</u> of the following three **bolded** verbatim statements (without quotation marks):

<u>If a product **does not** have FDA-approved patient labeling</u>:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

<u>If a product **has** FDA-approved patient labeling</u>:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

NO 28. A horizontal line must separate TOC from the FPI.

Comment: *Sponsor must include horizonal line.*

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

YES

30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

N/A 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use

Selected Requirements of Prescribing Information (SRPI)

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

NO 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment: *Sponsor included "section" prior to the numerical identifier (i.e. Section 5.2)*

YES 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

N/A 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

NO 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment: *Statement must be included.*

N/A 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

Patient Counseling Information

NO 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment: *Sponsor must provide the following verbatim statement:* See FDA-approved patient labeling (Medication Guide)

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/s/

TYREE L NEWMAN
05/20/2013

THERESA A CARIOTI
05/20/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

REVIEW DEFERRAL MEMO

Date:	March 27, 2012
To:	Ann Farrell, MD, Division Director **Division of Hematology Products (DHP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling Team **Division of Medical Policy Programs**
From:	Latonia M. Ford, RN, BSN, MBA Patient Labeling Reviewer **Division of Medical Policy Programs**
Subject:	Review Deferred: Medication Guide
Drug Name (established name):	Valchlor (mechlorethamine hydrochloride)
Dosage Form and Route:	Gel 0.02%
Application Type/Number:	NDA 202317
OSE RCM #:	2011-3131
Applicant:	Yaupon Therapeutics, Inc.

Reference ID: 3107267

This memorandum documents the deferral of our review of Valchlor (mechlorethamine hydrochloride) Gel 0.02%. On August 17, 2011, the Division of Hematology Products (DHP) requested that the Division of Medical Policy Programs (DMPP) review the proposed Medication Guide for New Drug Application (NDA) 202317 submitted by Yaupon Therapeutics, Inc.

Due to outstanding clinical findings DHP plans to issue a Complete Response (CR) letter. DHP determined that there were no links between the to-be-marketed product and the clinical trials for the proposed indication to treat (b) (4) Stage IA, IB (b) (4) mycosis fungoides type cutaneous T-cell lymphoma (CTCL) who have received at least one prior skin-directed therapy (b) (4)

Therefore, DMPP defers comments on the Applicant's proposed Medication Guide at this time. A final review will be performed after the Applicant submits a Complete Response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

LATONIA M FORD
03/27/2012

BARBARA A FULLER
03/27/2012

LASHAWN M GRIFFITHS
03/27/2012

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

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

Memorandum

Date: 3/26/2012

To: Tyree Newman, Regulatory Project Manager
Division of Hematology Products

From: James Dvorsky, Regulatory Reviewer
Division of Professional Promotion

Subject: Comments on draft labeling for Mechlorethamine Hydrochloride Gel 0.02%, NDA 202317

We acknowledge receipt of your September 12, 2011, consult request for the proposed product labeling (Package Insert (PI) for mechlorethamine hydrochloride, NDA 202317. OPDP notes that a Complete Response letter will be issued because there is no link between the to-be-marketed product and the clinical trials. The review team has not conducted any label reviews. Therefore, OPDP will not provide any comments at this time.

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/s/

JAMES S DVORSKY
03/26/2012

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: March 26, 2012

TO: Tyree Newman, Regulatory Project Manager
Angelo De Claro, M.D., Medical Officer
Albert Deisseroth, M.D., Team Leader
Division of Hematology Products (DHP)

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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

FROM: Anthony Orencia, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 202317

APPLICANT: Yaupon Therapeutics Inc.

DRUG: mechlorethamine hydrochloride (nitrogen mustard (b) (4))
NME: No

THERAPEUTIC CLASSIFICATION/REVIEW: Standard Review
INDICATION: Topical treatment of (b) (4) Stage IA, IB (b) (4) mycosis fungoides-type cutaneous T-cell lymphoma (CTCL) who have received at least one prior skin-directed therapy (b) (4)

CONSULTATION REQUEST DATE: October 6, 2011 (signed)
DIVISION ACTION GOAL DATE: May 27, 2012
PDUFA DATE: May 27, 2012

I. BACKGROUND:

The only approved topical therapy for mycosis fungoides is bexarotene. Previous treatments included PUVA, UVB and topical steroids.

Mechlorethamine (nitrogen mustard) is proposed as a topical therapy for early-stage mycosis fungoides type of cutaneous T-cell lymphoma. Some problems with the currently compounded mechlorethamine formulation include the following: (a) lack of data from controlled studies, (b) specific clear labeling instructions for use, (c) lack of quality standards about the compounded formulation leading to concerns about drug potency and stability, (d) low patient satisfaction with the compounded formulation. Due to problems with the compounded formulation of mechlorethamine, the proposed (b) (4) formulation may potentially be a suitable alternative.

A single adequate and well-controlled study was submitted in support of this NDA. Three clinical sites were audited, mainly based on higher enrollment.

Protocol 2005NMMF-201-US
This study was a multicenter, randomized, observer-blinded trial stratified by stage (IA versus IB and IIA) of daily topical application of the Yaupon mechlorethamine 0.02% gel versus mechlorethamine 0.02% compounded in Aquaphor. The objective of the study was to evaluate the efficacy and safety of topical application of nitrogen mustard 0.02% in a propylene glycol ointment (PG) versus nitrogen mustard 0.02% in an Aquaphor ointment (AP) in patients with Stage I or IIA mycosis fungoides. Diagnosis and disease staging of mycosis fungoides was based upon clinical and histological confirmation. The primary study endpoint was skin response determined by Composite Assessment of Index Lesion Severity (CAILS) following up to 12 months of treatment.

II. RESULTS (by protocol/site):

Name of CI	City, State	Protocol/Study Site#/# of subjects	Insp. Date	Final Classification
Madeleine Duvic, MD	Houston, TX	Protocol 2005NMMF-201-US Site #002 Subjects: 65	10/31-11/3, 2011	NAI
Matthew B. Zook, MD, PhD	Rockledge, PA	Protocol 2005NMMF-201-US Site #004 Subjects: 28	11/8-11/14, 2011	NAI

Bruce Strober, M.D., Ph.D. (original Principal Investigator)	New York, NY	Protocol 2005NMMF-201-US Site #007 Subjects: 18	1/17/-2/24, 2011	Pending (Preliminary: NAI)

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability
OAI = Significant deviations from regulations. Data unreliable/Critical findings may affect data integrity.
Preliminary= The Establishment Inspection Report (EIR) has not been received and findings are based on preliminary communication with the field.

CLINICAL STUDY SITE INVESTIGATOR

1. Madeleine Duvic, M.D. /Study Protocol 2005NMMF-201-US/Site #002
Houston, TX

a. What was inspected?
The inspection was conducted in accordance with Compliance Program 7348.811, from October 31 to November 3, 2011.

A total of 65 subjects were screened, 61 subjects were randomized and completed the study. An audit of 18 randomized subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms (CRFs), study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection
None.

c. General observations/commentary
Source documents, for randomized subjects whose records were audited, were verified against the CRFs and NDA subject line listings. No discrepancies were noted. There was no under-reporting of serious adverse events.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection.

d. Data acceptability/reliability for consideration in the NDA review decision.
Data submitted by this clinical site appear acceptable for this specific indication.

2. Matthew B. Zook, M.D., Ph.D./Study Protocol 2005NMMF-201-US/Site #002
Rockledge, PA

a. What was inspected?
The inspection was conducted in accordance with Compliance Program 7348.811, from November 8-14, 2011.

A total of 28 subjects were screened, 15 subjects were randomized, and 11 subjects completed the study. An audit of 15 randomized subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, CRFs, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection
None.

c. General observations/commentary
Source documents, for all of the subjects that were enrolled and randomized, were verified against the CRFs and NDA subject line listings. There was no under-reporting of serious adverse events noted.

This clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 was issued.

d. Data acceptability/reliability for consideration in the NDA review decision.
The data, in support of clinical efficacy and safety from this clinical site, appear acceptable for this specific indication.

3. Bruce Strober, M.D., Ph.D./ Study Protocol 2005NMMF-201-US/Site #007
New York, NY (Previous address during conduct of this study);
Farmington, CT (Present address)

a. What was inspected?
The inspection was conducted in accordance with Compliance Program 7348.811 from January 17 to February 24, 2012.

A total of 24 subjects were screened, 18 were randomized and 6 subjects completed the study [Note: 4 subjects were voluntarily withdrawn, 4 subjects were withdrawn due to

treatment-limiting toxicities, 1 subject was withdrawn due to an adverse event, 1 subject was withdrawn due to protocol violation for noncompliance and 2 subjects were lost to study follow-up].

All original informed consent documents were reviewed. An audit of 14 of 18 randomized subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, CRFs, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection
None.

c. General observations/commentary
Source documents, for randomized subjects whose records were audited, were verified against the CRFs and NDA subject line listings. There was no under-reporting of serious adverse events noted.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection.

Medical Officer Comments:
Per OSI consult and discussions with DHP, there was Sponsor-acknowledged incorrect randomization of 16 patients. The study coordinator at this clinical investigation site (Site #007) did not follow the randomization code. DHP wanted to verify the accuracy of the Sponsor's assessment during the clinical audit.

This error in randomization was acknowledged in the NDA submission to the Agency in Section 10.2 Protocol Deviations of the Clinical Study Report. This was also discussed during the Sponsor's application orientation face-to-face meeting with DHP on October 6, 2011. As acknowledged by the Sponsor and submitted in their NDA, this problem occurred exclusively at Site #007 and not systematically throughout the study. DHP also mentioned at that time, whether or not these 16 subjects (of 18 enrolled) at the New York University (NYU) Site #007 were included in the analyses, did not have any impact on the study efficacy.

The above finding was corroborated during two ORA field visits: (a) January 17-20, 2012 with the senior clinical research coordinator for Study Protocol 2005NMMF-201-US at Site #007 and (b) February 22, 2012, with Dr. Bruce Strober, the original principal investigator for this study (b) (4)

Per ORA field staff, the original study research nurse, who was the only study-unblinded member of this clinical trial investigation, did not follow proper procedures for randomization. The study-unblinded research nurse was involved in randomizing and dispensing of the test article. This original study research nurse assigned the PG formulation to all patients in stratum one with Stage 1A disease and AP formulation to all patients in stratum two with Stage 1B and IIA disease. This was discovered by another study-unblinded clinical research coordinator, who took over research responsibilities from the original research nurse, and reported the error to the originally study-blinded clinical site principal investigator, who then informed the Sponsor.

As part of the clinical site's preventive action plan per ORA, the Sponsor was notified and the NYU Dermatopharmacology Unit of the Department of Dermatology transferred all drug dispensation responsibilities to the NYU investigative pharmacy.

In summary, ORA confirmed that the error in randomization, noted by the Sponsor in their NDA submission and during the ORA clinical audit with Dr. Strober, was an isolated incident at Site #007 with respect to Study Protocol 2005NMMF-201-US.

d. Data acceptability/reliability for consideration in the NDA review decision.
DHP requested a clinical audit to confirm that randomization errors for 16 patients occurred. The errors were noted by the Sponsor and documented in the Sponsor's submission to the NDA, and also discussed during the Sponsor's application orientation meeting with DHP in October 2011. The field office was able to confirm that the randomization errors at NYU Site #007 took place.

Per DHP, DHP will make the determination as to the ultimate utility of the NYU #007 research data. In the most recent discussions with DHP, DHP advised OSI that the NYU Site #007 data may be considered for safety analysis. However, a final determination has yet to be made in this regard, as DHP proceeds to the later phases of their on-going NDA review.

With respect to the confirmed, Sponsor-reported errors in subject randomization noted for NYU Site #007, CDER OSI defers to DHP, regarding the decision of the ultimate disposition and use of these patient data.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical investigator sites were inspected in support of this application for Study Protocol 2005NMMF-201-US. No regulatory violations were noted or issued. Based upon review of inspectional findings for these clinical investigators, the study data collected appear generally reliable in support of the requested indication. OSI defers to DHP regarding the decision to include or exclude these known, incorrectly randomized patients, as identified in the NDA submission, in their final analyses and deliberations.

Note: Observations noted above are based on the preliminary communications from the field investigator for NYU Clinical Site #007; an inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

{See appended electronic signature page}

Anthony Orencia, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
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CONCURRENCE:

{See appended electronic signature page}

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Tejashri Purohit-Sheth, M.D.
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/s/

ANTHONY J ORENCIA
03/26/2012

JANICE K POHLMAN
03/26/2012

TEJASHRI S PUROHIT-SHETH
03/26/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	February 10, 2012
Application Type/Number:	NDA 202317
To:	Ann Farrell, MD, Director Division of Hematology Products
Through:	Todd Bridges, R.Ph., Team Leader Carol Holquist, R.Ph., Director Division of Medication Error Prevention and Analysis
From:	Kimberly DeFronzo, R.Ph., M.S., Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name and Strengths:	Valchlor (Mechlorethamine HCl) Gel 0.02%
Applicant/sponsor:	Yaupon Therapeutics, Inc.
OSE RCM #:	2011-3130

Reference ID: 3085849

1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis' (DMEPA's) evaluation of the proposed container label and carton labeling for Valchlor (Mechlorethamine HCl) Gel 0.02% (NDA 202317), submitted on December 7, 2011, and of the package insert, submitted on September 2, 2011, to identify vulnerability that could lead to medication errors.

1.1 BACKGROUND OR REGULATORY HISTORY

On July 27, 2011, Yaupon Therapeutics, Inc. submitted this application as a 505(b)(2) NDA for its topical formulation containing Mechlorethamine HCl (a.k.a. MCH, nitrogen mustard, NM). This product contains the same active substance found in Mustargen® for Injection (NDA#6695) which is being used as the Reference Listed Drug (RLD).

On August 17, 2004, Yaupon was granted Orphan designation for Mechlorethamine (nitrogen mustard) for the treatment of mycosis fungoides.

On May 31, 2006, Yaupon was granted Fast Track designation for topical nitrogen mustard (Mechlorethamine HCl) for the treatment of mycosis fungoides (cutaneous T-cell lymphoma) (b) (4)

On September 26, 2011, Yaupon was notified that the application was filed under the standard review classification.

On December 20, 2011, Yaupon was notified that FDA found the proposed proprietary name Valchlor acceptable (please see OSE Review # 2011-3818).

This product will be marketed under a REMS program currently under review.

1.2 PRODUCT INFORMATION

Valchlor (Mechlorethamine HCl) Gel 0.02% is an antineoplastic agent indicated for the topical treatment of (b) (4) Stage IA, IB (b) (4) mycosis fungoides type cutaneous T-cell lymphoma (CTCL) who have received at least one prior skin-directed therapy (b) (4) This product is to be applied with a thin film once daily to affected areas of the body on completely dry skin (at least 4 hours before or 30 minutes after showering). (b) (4) The amount of gel used for each application will depend upon the amount of the body surface area involved. This product is not a metered-dose product and will not be packaged with a measuring device to aid with proper dose administration.

If patients experience moderately-severe or severe dermatitis (erythematous skin with edema, vesiculation, bullae or necrosis at the site of application), they should suspend treatment with Valchlor. Upon improvement, treatment with Valchlor can be restarted at a reduced frequency of one application every other day or every third day and increased on a weekly basis to a maximum frequency of once daily as tolerated.

Valchlor is supplied as 60 g tube in a carton and contains 60 g of 0.02% mechlorethamine hydrochloride as a clear gel. It should be stored refrigerated.

Reference ID: 3085849

2 METHODS AND MATERIALS

Using Failure Mode and Effects Analysis[1] and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following to identify vulnerabilities that may lead to medication errors:

- Container Labels submitted December 7, 2011 - see Appendix A for image
- Carton Labeling submitted December 7, 2011 - see Appendix B for image
- Insert Labeling submitted September 2, 2011 (no image)

3 MEDICATION ERROR EVALUATION

The following sections discuss DMEPA's findings and analysis of the proposed labels and labeling for Valchlor (Mechlorethamine HCl) Gel 0.02%.

3.1 CONTAINER LABELS AND CARTON LABELING

The container labels and carton labeling use the term "dermatologic" to define the route of administration. However, the term "dermatologic" is not referenced in the CDER Data Standards Manual as a defined route of administration. Therefore, maintaining the term "dermatologic" in the route of administration statement (i.e. For Topical Dermatologic Use Only) makes this product inconsistent with other topical products because the route of administration of other products appears as "For Topical Use Only". Additionally, the insert labeling does not use the term "Dermatologic" to define the route of administration, instead the terms "Topical Dermatologic***al*** Use Only' (b) (4) is used for this expression. Because this is not an overt safety issue, DMEPA defers to DDDP to whether or not the words 'Dermatologic' and/or 'Dermatological' should be removed from the route of administration expression.

3.2 INSERT LABELING

The dosage form and route of administration is not consistently presented throughout the labels and labeling. For example: In the (b) (4) Full Prescribing Information under the Dosage and Administration section, it states "For Topical Dermatological Use Only" (b) (4) It is important to be consistent with the presentation of the route of administration throughout the label and labeling to help prevent confusion leading to wrong route of administration errors.

As previously mentioned in section 3.1, DMEPA defers to DDDP for the final decision regarding the expression of the route of administration.

---

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

Reference ID: 3085849

3.3 PRODUCT TRANSFER

Due to the potential safety risk posed by the high probability of this product for accidental transfer from the patient onto other people, a meeting with the Division was held on January 13, 2011, to discuss the need for a transference study that may alleviate safety concerns arising from this possibility. The Division determined that the Applicant has provided sufficient evidence to support the lack of systemic absorption of this product. Moreover, due to the instability of the mechlorethamine molecule in this formulation, serious skin irritation is not expected to result from accidental skin absorption of the product. This is further supported by the lack of serious skin irritation reported during the clinical trial phase of the development of this product. Therefore, the safety risk from accidental transfer and resultant skin absorption was assessed to be negligible and a transference study was deemed to be unnecessary.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling are unacceptable and introduce vulnerability that can lead to medication errors. We provide recommendations to the Division in Section 4.1 and to the Applicant in Section 4.2. We recommend these revisions be made to the label and labeling prior to approval of the product.

If you have further questions or need clarifications, please contact Sue Kang, OSE Project Manager, at 301-796-4216.

4.1 COMMENTS TO THE DIVISION

A. General Comments

The route of administration is inconsistently expressed across the products labels and labeling. For example: In the (b) (4)

Full Prescribing Information under the Dosage and Administration section, it states "For Topical Dermatological Use Only" (b) (4)

It is important to be consistent with the presentation of the route of administration throughout the label and labeling to help prevent confusion leading to wrong route of administration errors. Therefore, please ensure the route of administration is consistently presented throughout the labels and labeling.

B. Insert Labeling

1. We recognize that the Applicant uses symbols (e.g., >, ≥) in the insert labeling. The symbols > and ≥ appear on the ISMP list of Error-Prone Abbreviations, Symbols, and Dose Designations. On June 14, 2006, the Agency, in conjunction with ISMP, launched a campaign to warn healthcare practitioners and consumers not to use error-prone abbreviations, acronyms, dose designations such as trailing zeros, or symbols. As part of this campaign, FDA agreed not to use such error

prone designations in their approved product labeling because they are carried onto the prescribing practice. Therefore, we recommend using the terms "greater than" or "greater than or equal to", respectively, instead of the symbols as they have been mistaken as the opposite of its intended meaning and practitioners have mistakenly used the incorrect symbol.

2. The Dosage and Administration section in the Highlights of the Prescribing Information is missing the "dose" in its instructions since there is no reference to how much product the patient should apply to their skin.
3. The Dosage and Administration and Patient Counseling Information sections in the Full Prescribing Information recommend patients apply a "thin film" of Valchlor. However, "thin" is an ambiguous term and should be further delineated such as "using enough to cover the entire area with a thin film".
4. The Dosage Forms and Strengths section in the Prescribing Information is missing the dosage form "gel".
5. The (b) (4) designation should be deleted (b) (4)
6. The storage statement in the Storage and Handling Section in the Full Prescribing Information discussion needs to be revised (b) (4) to be consistent with USP standards. In addition, warning information should be provided regarding freezing of the product.
7. Due to the potential for accidental secondary exposure of household members, patients should be provided with explicit instructions on the proper disposal of gloves, and other related items, in the Patient Counseling Information section of the Full Prescribing Information (similar to what is provided in the Medication Guide). In addition, instructions on how to launder contaminated clothing should also be provided in both the Full Prescribing Information and Medication Guide for consistent messaging to the patients.
8. Furthermore, consideration should be given to providing warning/precaution regarding secondary exposure from humans as well as objects (similar to testosterone gel products).

C. Medication Guide

1. Delete the statement (b) (4)
2. Consider revising the phrase (b) (4) to a plain language alternative that patients may better understand.
3. Include instructions on how to handle and launder contaminated clothing in addition to proper disposal of gloves, and other related items.

4.2 COMMENTS TO THE APPLICANT

A. General Comments for the Container Label & Carton Labeling

1. Ensure the prominence of the established name (including the dosage form "gel") is at least ½ the size of the proprietary name taking into account typography, layout, contrast, and other printing features to ensure it has prominence commensurate with the proprietary name as per 21 CFR 201.10(g)(2).
2. (b) (4)
3. Increase the prominence of the route of administration statement (including the "Avoid contact with eyes, mouth, and other mucous membranes" statement) by using different font size and/or color and relocating the statements to the center of the principal display panel.
4. Increase prominence of the storage condition statement to highlight the refrigeration of this product since it is different from other topical products that are typically stored at room temperature.
5. Revise the storage statement (b) (4) to be consistent with USP standards. In addition, warning information should be provided regarding freezing of the product.
6. Delete or minimize (b) (4)
7. Delete or change (b) (4)

B. Container Label

1. Ensure the lot number and expiration date is clearly noted on the container as per 21 CFR 211.130(c) and 21 CFR 201.17.
2. Reduce the font size and unbold the "Rx Only" statement to decrease its prominence and avoid competing with other important information.

C. Carton Labeling

1. Delete or minimize (b) (4)
2. Correct the typo in the statement (b) (4) on the back panel.
3. Relocate the reference regarding the Medication Guide from the side panel to the principal display panel to increase its prominence.

Appendix A:

Container Label

Appendix B:

Carton Labeling

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

/s/

KIMBERLY A DE FRONZO
02/10/2012

TODD D BRIDGES
02/10/2012

CAROL A HOLQUIST
02/10/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 202317	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: Mechlorethamine Hydrochloride Dosage Form: Gel Strengths: 0.02%		
Applicant: Yaupon Therapeutics Inc. Agent for Applicant (if applicable):		
Date of Application: 7/27/2011 Date of Receipt: 7/27/2011 Date clock started after UN:		
PDUFA Goal Date: 5/27/2012	Action Goal Date (if different):	
Filing Date: 9/25/2011 (Sunday)	Date of Filing Meeting: 9/1/2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5		
Proposed indication(s)/Proposed change(s): Treatment of mycosis fungoides (cutaneous T-cell lymphoma) (b) (4)		

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

Reference ID: 3020554

☒ Fast Track 5/31/2006 ☐ Rolling Review ☒ Orphan Designation 8/17/2004 ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*): N/A	
List referenced IND Number(s): IND 067839	

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

Reference ID: 3020554

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

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

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

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

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

Reference ID: 3020554

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

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

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

Reference ID: 3020554

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

Reference ID: 3020554

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

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:			**X**	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			505(b)(2) application requesting approval of a new indication
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			Full waiver requested
If studies or full waiver not included, is a request for full			X	

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

Reference ID: 3020554

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

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in				

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

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

Reference ID: 3020554

the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?		X		
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)		X		
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?		X		
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***		X		
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 12/14/2005 ***If yes, distribute minutes before filing meeting***	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 2/26/10 (non-clinical); 3/4/10 (CMC); 12/21/10 (Clinical) ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs) **Date:** 2/17/2009	X			

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If yes, distribute letter and/or relevant minutes before filing meeting				

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 1, 2011

NDA: 202317

PROPRIETARY NAME: N/A

ESTABLISHED/PROPER NAME: Mechlorethamine Hydrochloride

DOSAGE FORM/STRENGTH: Gel; 0.02%

APPLICANT: Yaupon Therapeutics, Inc.

PROPOSED INDICATION: Treatment of mycosis fungoides (cutaneous T-cell lymphoma) (b) (4)

BACKGROUND: This NDA has been submitted as a 505(b)(2). It is requesting approval of a new indication based on 2 clinical studies. The RLD for this application is NDA 6695, Mustargen, a cytoxic alkylating agent approved on 3/15/1949, for Lundbeck Inc. There are no unexpired patents or exclusivities for this product.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Modupe Fagbami (filing) Tyree Newman	N Y
	CPMS/TL:	Frank Cross Jr. (filing) Janet Jamison	Y N

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Cross-Discipline Team Leader (CDTL)	Al Deisseroth		Y
Clinical	Reviewer:	Robert White (filing)/ Angelo De Claro	Y Y
	TL:	Al Deisseroth	Y
Social Scientist Review (*for OTC products*) N/A	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*) N/A	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*) N/A	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Julie Bullock	Y
	TL:	Brian Booth	N
Biostatistics	Reviewer:	Yun Wang	Y
	TL:	Mark Rothmann	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Alex Putman (filing) Yash Chopra	Y N
	TL:	Haleh Saber	Y
Statistics (carcinogenicity) N/A	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements) N/A*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Anne Marie Russell Gaetan Ladouceur	Y Y
	TL:	Janice Brown	Y
Quality Microbiology *(for sterile products)*	Reviewer:	Stephen Langille	N
	TL:	James Mcvey	N
CMC Labeling Review	Reviewer:	Anne Marie Russell	Y

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		Gaetan Ladouceur	Y
	TL:	Janice Brown	Y
Facility Review/Inspection	Reviewer:	Anne Marie Russell Gaetan Ladouceur	Y Y
	TL:	Janice Brown	Y
OSE/DMEPA (proprietary name)	Reviewer:	Loretta Holmes	N
	TL:	Irene Chang	N
OSE/DRISK (REMS)	Reviewer:	Latonia Ford	Y
	TL:	Barbara Fuller	N
OC/DCRMS (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS) N/A	Reviewer:		
	TL:		
Biopharmaceutics	Reviewer:	Tapash Ghosh	N
	TL:	Angelica Dorantes	N
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable

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CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? 4 sites **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☐ NO ☒ To be determined Reason:
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

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Comments:	☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **N/A** **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☒ YES ☐ NO

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Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Ann Farrell, M.D.

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

Comments: Fileable per email of 9/6/2011

REGULATORY CONCLUSIONS/DEFICIENCIES

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

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ACTIONS ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

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Appendix A (NDA and NDA Supplements only)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

/s/

MODUPE O FAGBAMI
09/26/2011

FRANK H CROSS
09/26/2011