CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202317Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 202317 SUPPL # N/A HFD # 160

Trade Name Valchlor

Generic Name mechlorethamine gel 0.016%

Applicant Name Ceptaris Therapeutics (formerly Yaupon Therapeutics)

Approval Date, If Known August 23, 2013

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(2)

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

YES ☒ NO ☐

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

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

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d) Did the applicant request exclusivity?

YES ☐ NO ☒

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

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).
NDA# 6695 (Mustargen)

Reference ID: 3363189

2. Combination product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

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

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the

Reference ID: 3363189

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

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

YES ☒ NO ☐

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

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

YES ☐ NO ☒

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

YES ☐ NO ☒

If yes, explain:

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

YES ☐ NO ☒

If yes, explain:

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

Reference ID: 3363189

2005NMMF-201-US - A Phase II Pivotal Trial to Evaluate the Safety and Efficacy of Nitrogen Mustard (NM) 0.02% Ointment Formulations in Patients with Stage I or IIA Mycosis Fungoides (MF)

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

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

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

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

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

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

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

Reference ID: 3363189

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

2005NMMF-201-US - A Phase II Pivotal Trial to Evaluate the Safety and Efficacy of Nitrogen Mustard (NM) 0.02% Ointment Formulations in Patients with Stage I or IIA Mycosis Fungoides (MF)

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 ! !
IND # 067839 YES ☒ ! NO ☐
! Explain:

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

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 ! !

Reference ID: 3363189

YES ☐	! NO ☐
Explain:	! Explain:

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

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

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Tyree Newman
Title: Regulatory Health Project Manager
Date: August 26, 2013

Name of Division Director signing form: Ann Farrell
Title: Division Director, DHP, OHOP

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

Reference ID: 3363189

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

/s/

TYREE L NEWMAN
08/26/2013

ANN T FARRELL
08/26/2013

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 202317 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DHP PDUFA Goal Date: 5/27/12 Stamp Date: 7/27/2011

Proprietary Name: Valchlor

Established/Generic Name: mechlorethamine HCl

Dosage Form: Gel

Applicant/Sponsor: Ceptaris Therapeutics (formerly Yaupon Therapeutics)

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Treatment of mycosis fungoides (cutaneous T-cell lymphoma) [redacted] (b) (4).

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☒ indication(s); ☒ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☒ Yes. PREA does not apply. **Skip to signature block.**

☐ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

☐ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda hhs.gov) OR AT 301-796-0700.

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed∆
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
- ☐ No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed∆
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

∆ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

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

/s/

TYREE L NEWMAN
05/02/2012

1.3.3 DEBARMENT CERTIFICATION

FDA makes available a separate list of firms or persons debarred pursuant to the debarment provisions of the Federal Food, Drug, and Cosmetic Act located at http://www.fda.gov/ora/compliance_ref/debar/default.htm. The names of principal investigators and subinvestigators involved in clinical research sponsored by Yaupon Therapeutics, Inc. have been checked against this list to assure that investigators are permitted to conduct clinical investigations for the company.

Yaupon Therapeutics, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Lisa Wittmer

Lisa Wittmer, M.S., Ph.D.
Vice President, Regulatory Affairs
Yaupon Therapeutics, Inc.

13 July 2011
Date

Reference ID: 3367073

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 202317 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Valchlor Established/Proper Name: mechlorethamine 0.016% Dosage Form: gel		Applicant: Ceptaris Therapeutics, Inc./ (formerly) Yaupon Therapeutics, Inc. Agent for Applicant (if applicable):
RPM: Tyree Newman		Division: DHP

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

NDA 6695 for Mustargen (mechlorethamine hydrochloride) injection, 10 mg/vial

Provide a brief explanation of how this product is different from the listed drug.

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

☐ This application does not reply upon a listed drug.
☒ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☒ No changes ☐ Updated Date of check: 8/23/13

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is August 27, 2013	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None CR - 5/4/12

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☒ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☒ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

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

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ 21 CFR 314.50(i)(1) ☒ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☒ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☒ N/A (no paragraph IV certification) ☐ Verified

Version: 6/14/13

• [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for **each** paragraph IV certification:	
(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).	☐ Yes ☐ No
*If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*	
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?	☐ Yes ☐ No
*If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.* *If "**No**," continue with question (3).*	
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).	☐ Yes ☐ No
*If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*	
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?	☐ Yes ☐ No
*If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**No**," continue with question (5).*	

Reference ID: 3362355

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[4]	8/23/2013
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) AP – 8/23/13, CR - 5/4/12
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	8/21/13
• Original applicant-proposed labeling	2/27/13, 7/27/11
• Example of class labeling, if applicable	Mustargen

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

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❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	8/6/13
• Original applicant-proposed labeling	2/27/2013, 7/27/2011
• Example of class labeling, if applicable	N/A
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	7/29/13
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	6/26/13, 12/20/11 (accepted) 6/26/13, 12/20/11
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 5/20/13 ☒ DMEPA 7/22/13, 2/10/12 ☒ DMPP/PLT (DRISK) 6/21/13, 3/27/12 ☒ ODPD (DDMAC) 6/25/13, 3/26/12 ☐ SEALD ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	9/26/11 ☐ Not a (b)(2) 7/23/13, 4/9/12 ☐ Not a (b)(2) 8/23/13
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC N/A If PeRC review not necessary, explain: Orphan Designation • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included

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

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	8/21/13, 8/16/13, 8/8/13, 8/6/13, 8/2/13, 7/31/13, 7/22/13, 7/18/13, 7/3/13, 6/27/13, 6/25/13, 6/24/13, 6/21/13, 5/21/13, 4/17/12, 4/13/12, 1/11/12, 1/9/12, 1/5/12, 12/1/11, 11/15/11, 11/3/11, 9/29/11, 9/28/11, 9/27/11, 9/26/11, 9/21/11, 9/16/11, 9/8/11, 9/7/11, 8/30/11, 8/29/11, 8/26/11
❖ Internal memoranda, telecons, etc.	7/15/13 (tcon), 12/16/11 (tcon), 12/8/11 (tcon)
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 12/21/10 (Clinical), 3/4/10 (CMC), 2/26/10 (non-clinical)
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	N/A
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 8/22/13, 5/3/12
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 8/12/13, 4/24/12
PMR/PMC Development Templates *(indicate total number)*	☐ None 1
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	4/11/12 (Co-signed Primary review dated 3/28/12)
• Clinical review(s) *(indicate date for each review)*	6/25/13, 3/28/12, Filing checklist-9/7/11
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See 6/25/13 Clinical review, p.8 See 3/28/12 Clinical review, p.14
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None 6/25/13 (Pharmacovigilance)

[6] Filing reviews should be filed with the discipline reviews.

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❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☐ None 7/18/13, 3/12/12
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested Letters - 4/13/12, 2/6/12, 1/5/12 Inspection review - 3/26/12
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None 6/25/13, 4/19/12 (Co-signed primary reviews dated 6/25/13, 4/18/12)
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None 6/25/13, 4/19/12(Co-signed primary reviews dated 6/25/13, 4/18/12)
Statistical Review(s) *(indicate date for each review)*	☐ None 6/25/13, 4/18/12, Filing checklist - 9/2/11
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None 7/9/13, 3/23/12 (Co-signed primary reviews dated 7/8/13, 3/23/12)
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 7/8/13, 3/23/12, Filing checklist - 9/9/11
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None 4/27/12 (Co-signed Supervisory review dated 4/26/12)
• Supervisory Review(s) *(indicate date for each review)*	☐ None 4/19/13 (Co-signed primary review dated 4/19/13); 4/26/12
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 4/19/13, Filing checklist - 9/2/11
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Reference ID: 3362355

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None 8/20/13
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None 8/19/13 (Co-signed primary review addendum dated 8/19/13), 8/8/13, 8/1/13 (Co-signed primary review dated 8/1/13), 4/24/12 (Co-signed primary review addendum dated 4/22/12), 4/20/12 (Co-signed primary review dated 4/20/12)
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 8/19/13 (addendum), 8/1/13, 4/22/12 (addendum), 4/20/12, Filing checklist- 9/8/11
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 8/14/13, 3/26/12, Filing checklist- 9/8/11
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	4/20/12 (See Product Quality review, p. 59)
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: 11/16/11 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

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

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

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

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

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

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

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

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

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

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

Reference ID: 3362355

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/s/

TYREE L NEWMAN
08/23/2013

MEMORANDUM OF TELECONFERENCE

Date: August 20, 2013

Subject: NDA 202317 (Valchlor) – Package Insert Labeling discussions

FDA Attendees (Agency):

Ann Farrell, M.D., Director
Edvardas Kaminskas, M.D., Deputy Director
R. Angelo De Claro, M.D., Medical Officer Team Leader
Lie Nie, Ph.D., Statistician
Robert Kane, M.D., Deputy Director, Safety
Alexandria Schwarsin, M.D., Medical Reviewer
Tyree Newman, Regulatory Project Manager

Ceptaris Therapeutics (Sponsor):

Lisa Wittmer, Ph.D. Vice President, Global Regulatory Affairs
Tim Henkel, MD, Executive Vice President, Head of Research and Development
Jaci Yeager, Regulatory Affairs Associate
Kelly Copeland, Vice President, Product Strategy

Background:

On August 13, 2013, Ceptaris requested to have a teleconference with the Agency for NDA 202317. The purpose of the call was to reach an agreement on the remaining issues identified in the August 19, 2013, package insert submitted by Ceptaris to the Agency.

Discussion Items:

- Ceptaris requested to discuss the following issues with the Agency:
    - Section 1 – In the Indications and Usage section, Ceptaris wanted to discuss why the Agency was in disagreement with the following proposed indication statement, "*VALCHLOR is an alkylating drug indicated for the topical treatment of Stage IA and IB mycosis fungoides-type cutaneous T-cell lymphoma in adult patients who have received prior skin-directed therapy.* (b) (4)).

      Agency Response –The Agency stated that the indication and usage is based on what occurred in the clinical trial setting, therefore the patient population identified in the indication section of the labeling should be consistent with the patient population that was observed in

the clinical setting. (b) (4)

- Section 6 – In the Adverse Reaction section, Ceptaris requested to include the following statement (b) (4)

  Agency Response – The Agency stated this statement should be removed (b) (4)

- Section 14 - In the Clinical Studies section of the prescribing information, Ceptaris proposed (b) (4)

  Agency Response – The Agency stated that (b) (4) **was not necessary** (b) (4)

Action Items:

The Agency will make edits to the August 19, 2013, version of the package insert submitted by Ceptaris addressing the issues that were discussed and agreed upon during the teleconference and forward to Ceptaris for review.

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/s/

TYREE L NEWMAN
08/22/2013

Newman, Tyree

From: Newman, Tyree
Sent: Wednesday, August 21, 2013 9:18 AM
To: lwittmer@ceptaris.com
Subject: NDA 202317 - Labeling Advice

Good morning Lisa, please see the attached package insert and medication guide for NDA 202317 in tracked changes for your review.

Please review the FDA's edits and using the same draft, do the following:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you do not agree with the labeling revisions, provide your comments and proposed language (shown in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

If you agree with all of the changes, then please submit the final version of the labeling (package insert and medication guide) to your NDA.

In addition, please review the document for formatting.

Please submit the revised package insert and medication guide to me by today close of business.

Please confirm receipt of this e-mail. If you have any questions, feel free to contact me.

Kind regards,

Tyree

Tyree Newman
Sr. Regulatory Health Project Manager
Food and Drug Administration
Office of New Drugs
Immediate Office
Therapeutics Biologics and Biosimilars Team
10903 New Hampshire Ave.
Silver Spring, MD 20993
301-796-3907 (phone)
Tyree.Newman@fda.hhs.gov

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/s/

TYREE L NEWMAN
08/21/2013

Newman, Tyree

From:	Higgins, Janet
Sent:	Friday, August 16, 2013 12:35 PM
To:	lwittmer@ceptaris.com
Cc:	Newman, Tyree
Subject:	Revised label for your NDA 20317: VALCHLOR™ respond by Monday 2pm EST, August 19, 2013
Attachments:	NDA 202317 Proposed labeling 9Aug13_final tracked_DHP.DOC; NDA 202317 Medication Guide 9Aug13_final tracked_DHP.DOC

Good Afternoon Dr. Wittmer,

Please refer to the attached revised label for your NDA 20317: VALCHLOR™. Please respond by **Monday 2pm EST, August 19, 2013**(in track change version). It is also necessary to submit officially to the NDA on Monday, August 19, 2013.

Sincerely,

Janet Higgins on behalf of Tyree Newman

Janet G. Higgins
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2331
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/s/

TYREE L NEWMAN
08/19/2013

Newman, Tyree

From: Newman, Tyree
Sent: Wednesday, July 31, 2013 4:51 PM
To: 'lisa wittmer'
Cc: Jaci Yeager
Subject: RE: NDA 202317: Tube labels and Carton advice
Attachments: 10726dft 04-19-13.pdf

Good afternoon Lisa, in response to your July 29, 2013, email inquiring about the rationale for the proprietary name to appear in title case on the container label and carton labeling. The review team has referenced guidance that supports the use of title case for optimizing the readability of the name. This recommendation can be found in the attached Labeling Guidance for Industry, "Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors".

Please inform me if you have any additional questions.

Kind regards,

Tyree

Tyree Newman
Sr. Regulatory Health Project Manager
Food and Drug Administration
Office of New Drugs
Immediate Office
Therapeutics Biologics and Biosimilars Team
10903 New Hampshire Ave.
Silver Spring, MD 20993
301-796-3907 (phone)
Tyree.Newman@fda.hhs.gov

From: lisa wittmer [mailto:lwittmer@ceptaris.com]
Sent: Monday, July 29, 2013 4:21 PM
To: Newman, Tyree
Cc: Jaci Yeager
Subject: RE: NDA 202317: Tube labels and Carton advice

Hi Tyree,
Thank you for your email. I have left you a voicemail message. The examples I mentioned on the voicemail message are: VIBATIV®, PROCYSBI®, RIXUBIS®, ILARIS®, RAVICTI® and XGEVA®.
Lisa

From: Newman, Tyree [mailto:Tyree.Newman@fda.hhs.gov]
Sent: Monday, July 29, 2013 3:34 PM
To: lisa wittmer
Cc: Jaci Yeager
Subject: NDA 202317: Tube labels and Carton advice

Reference ID: 3356818

Good afternoon Lisa, your edits to the carton and container labeling sent to us on July 26, 2013, are under review however, the review team wanted to advise you of the following:

We continue to recommend that you revise the proprietary name to appear in title case (e.g. Valchlor) on the container labels and carton labeling.

Please inform me if you have any questions.

Kind regards,

Tyree

Tyree Newman
Sr. Regulatory Health Project Manager
Food and Drug Administration
Office of New Drugs
Immediate Office
Therapeutics Biologics and Biosimilars Team
10903 New Hampshire Ave.
Silver Spring, MD 20993
301-796-3907 (phone)
Tyree.Newman@fda.hhs.gov

From: lisa wittmer [mailto:lwittmer@ceptaris.com]
Sent: Friday, July 26, 2013 2:01 PM
To: Newman, Tyree
Cc: Jaci Yeager
Subject: NDA 202-317: Tube labels and Carton artwork

Tyree,
Please find attached the updated tube labels and carton artwork. Your prior email dated July 22, 2013 references an example of FDA's required format for presentation of the brand/common name, but there was no example included. Nonetheless, Ceptaris has adjusted the logo according to FDA's suggestions and increased the font size of the common name so that the lower case letters measure half of the size of the brand name letters. In addition to addressing FDA's comments, we have made other changes to make the text consistent with FDA's feedback on the PI and Med Guide and added the list of inactive ingredients (in alphabetical order). We will submit these formally on Monday. Please let me know if you have any questions.
Lisa

Lisa Wittmer

Lisa Wittmer
Vice President, Global Regulatory Affairs
Ceptaris Therapeutics, Inc.
101 Lindenwood Drive, Suite 400
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Mobile: 484-431-7991
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Reference ID: 3356818

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APPEARS THIS WAY ON ORIGINAL

Guidance for Industry

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov/. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER), Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis, Carol Holquist at 301-796-0171.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

April 2013
Drug Safety

Guidance for Industry

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors

Additional copies are available from:

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

April 2013
Drug Safety

Reference ID: 3356818

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Guidance for Industry[1]

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The purpose of this guidance is to help prescription drug and biologic product manufacturers minimize medication errors[2] associated with their products. This guidance focuses on safety aspects of the container **label**[3] and carton **labeling** design, and provides a set of principles and recommendations for ensuring that critical elements of a product's container labels and carton labeling are designed to promote safe dispensing, administration, and use of the product.

This guidance applies to prescription drug and CDER-regulated biological products, including the following:

- Prescription drug products marketed under an approved new drug application (NDA) or abbreviated new drug application (ANDA);
- Prescription drugs marketed without an approved NDA or ANDA; and
- Biological products marketed under an approved biologics licensing application (BLA).

In this guidance, all such products are jointly referred to as *products*, and persons responsible for designing product container labels and carton labeling are referred to as *sponsors*. References to ***end user(s)*** include, but are not limited to, the patient, patient's caregiver, the prescribing physician, nurse, pharmacist, pharmacy technician, and other individuals who are involved in routine procurement, stocking, storage, and administration of medications (e.g., medication technicians).

[1] This guidance was prepared by the Division of Medication Error Prevention and Analysis in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.
[2] A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer (National Coordinating Council for Medication Error Reporting and Prevention, http://www.nccmerp.org/aboutMedErrors.html).
[3] Terms that appear in bold type upon first use are defined in the Glossary section of this guidance.

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This guidance does not apply to over-the-counter (OTC) drug products.

This is the second in a series of three guidance documents that the Food and Drug Administration (FDA) is issuing to help minimize medication errors. The first guidance focuses on minimizing risks associated with the design of the drug product and its **container closure system**.[4] The third planned guidance will focus on best practices for the development and testing of proposed **proprietary names** to minimize risks associated with drug product nomenclature, such as proprietary names that look or sound like the name of another product (e.g., look-alike or sound-alike names).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

Medication errors are a significant public health concern that account for an estimated 7,000 deaths annually in the United States.[5] In July 2006, the Institute of Medicine (IOM) published a report titled *Preventing Medication Errors.* The report cited labeling and **packaging** issues as the cause of 33 percent of all medication errors and 30 percent of fatalities from medication errors.[6] The IOM emphasized that "[p]roduct naming, labeling, and packaging should be designed for the end user — the provider in the clinical environment and/or the consumer."[7] More specifically, the report urged FDA to address safety issues related to product labeling and nomenclature using the principles of cognitive and human factors engineering.[8]

On September 27, 2007, the reauthorization and expansion of the Prescription Drug User Fee Act (PDUFA IV) was signed into law as part of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85). As part of the PDUFA IV reauthorization, FDA committed to certain performance goals, including measures to reduce medication errors related to look-alike and sound-alike proprietary names, unclear label abbreviations, acronyms, dose

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[4] See the FDA draft guidance for industry *Safety Considerations for Product Design to Minimize Medication Errors* (December 2012). When final, this guidance will represent FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default htm.

[5] Phillips DP, Christenfeld N, and Glynn LM. Increase in US Medication-Error Deaths between 1983 and 1993. The Lancet. 351:643-644, 1998.

[6] Aspden P, Wolcott JA, Bootman JL, Cronenwett LR, eds. *Preventing Medication Errors*. Institute of Medicine, The National Academies Press: Washington DC. 2006. Chapter 6: p. 275.

[7] IOM, *Preventing Medication Errors*. Chapter 6, Recommendation 4, p. 280.

[8] IOM, *Preventing Medication Errors.* Chapter 6, Actions to Improve Drug Naming, Labeling, and Packaging, p. 281-282.

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designations, and error-prone labeling and packaging designs.[9] In June 2010, FDA held a public workshop and opened a public docket to receive comments on these topics.[10] This guidance and the companion guidances described in section I of this guidance present FDA's recommendations and conclusions after reviewing this public input.

III. GENERAL CONSIDERATIONS

The format and content of prescription drug and biological product labels and labeling must comply with FDA regulations in 21 CFR part 201 for drugs and 21 CFR part 610 Subpart G-Labeling Standards for biologics, and should conform with all labeling requirements required by the United States Pharmacopeia (USP). Although this guidance refers to some aspects of those requirements as they relate to the prevention of medication errors, product sponsors should refer to the regulations and USP for the full requirements.

A. Poor Design of Product Container Labels and Carton Labeling Can Obscure Critical Safety Information

Product container labels and carton labeling should communicate information that is critical to the safe use of a medication from the initial prescription, to procurement, preparation and dispensing of the product to the time it is given to the patient. Poor label design can contribute to medication errors by making it difficult for healthcare professionals, caregivers, and/or patients to readily locate and understand critical safety information. Examples from reports of medication errors include:

- Key information, such as the product name, strength, and dosage form, is missing; is expressed in a confusing manner; or is not prominently located and displayed.
- Key information does not appear in the same field of vision (i.e., the information is not readable without having to turn or rotate the container).
- Container labels and carton labeling look similar across multiple strengths of the same product or across multiple products within a company's product line.
- Container labels and carton labeling look similar among multiple products from different manufacturers.
- Container labels and carton labeling are visually cluttered by extraneous text or distracting images and graphics.
- Error-prone abbreviations or symbols are used.

[9] See letters from the Secretary of Health and Human Services to the Chairman of the Committee on Health, Education, Labor, and Pensions of the Senate and the Chairman of the Committee on Energy and Commerce of the House of Representatives, as set forth in the Congressional Record http://www fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119243.htm.

[10] See April 12, 2010, Workshop Notice and Request for Comments (75 FR 18514), Docket No. FDA-2010-N-0168.

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- Text is difficult to read because of font size or style, insufficient color contrast, or other design elements.

- Overlapping text is printed on both sides of a clear, transparent, or translucent container label such as those that might be found on syringes, ampules, vials, intravenous bags or low-density polyethylene (LDPE) vials.

B. Risk Assessment During the Design Stage Can Reduce the Risk of Medication Errors

It is important to consider the end users and their environment of use during the development and design of a drug product's label, labeling, and packaging. Sponsors should assess and minimize the risk of medication errors resulting from the design of product container labels and carton labeling before submitting proposed labels and labeling for FDA review and approval. Medication error risk assessment should take into account all of the prospective end users and the environments in which the product will be prescribed, dispensed, and used. FDA recommends applying the principles described in this guidance and testing the overall design using well-established risk assessment methods at the pre-IND stage or during the early stages of label, labeling, and packaging development, and when changes or additions to an already marketed drug product occur throughout the product's life cycle. For more information and recommendations on analytical methods for risk assessments, we refer you to the FDA draft guidance for industry *Safety Considerations for Product Design to Minimize Medication Errors* (see footnote 4).

C. Critical Product Information Should Appear on the Principal Display Panel

The **principal display panel** (PDP) is the panel of a label that is most likely to be displayed, presented, shown, or examined by the end user. We recommend that the PDP include the following critical information:

- Proprietary name
- **Established name** or **proper name**
- Product strength
- Route(s) of administration
- Warnings (if any) or cautionary statements (if any)

The information listed above should be the most prominent information on the PDP. Other information on the PDP such as the Rx-only statement, net quantity statement, manufacturer name, and logo should not compete in size and prominence with the important information listed above. Information such as the product strength equivalency statement, "each tablet contains" statement, and manufacturer name and logo is best placed on the side or back panel to maximize the prominence of the important information listed above.

D. Labels Should be Legible, Readable, and Easy to Understand

Reference ID: 3356818

FDA recommends that the text on the container label and carton labeling should be (1) generally oriented in the same direction; (2) placed in the same field of vision (i.e., readable without having to turn or rotate the container); and (3) surrounded by adequate white space to improve **readability** and avoid crowding. For FDA regulations related to the readability of product labels, see 21 CFR 201.15. Important factors to consider include the following:

1. Container Label Size

The size of the container label greatly influences the overall container label design. FDA recognizes that in certain circumstances the container closure system might actually be inseparable from the container label (e.g., LDPE vial, glass ampule, syringe, blister foil backing, and intravenous bag). In other cases, the container label might be a paper, foil, or clear label that is affixed to the container closure system or blister. If the container label is too small, important information may not always fit on the principal display panel of the container label.

Ideally, manufacturers should explore approaches to create larger container labels or unique packaging to accommodate all critical information on the immediate product container label. FDA regulations provide an exemption from some drug labeling requirements when the container is too small or otherwise unable to accommodate a label with enough space to include all required information, provided that all required information is present on the carton labeling or in the prescribing information (21 CFR 201.10(i)). In such cases, the container label must include at minimum the product's proprietary and established name (if any); product strength; lot number; and the name of the manufacturer, packer, or distributor. USP requires the label of an **official drug product** to bear an expiration date.[11] Therefore, we also strongly recommend including the product's expiration date. For biological products, at a minimum, the name of the product, lot number, manufacturer name, and the recommended individual dose for multiple-dose containers must be included (21 CFR 610.60(c)). Such exemptions are not available, however, if the lack of space is caused by failure to use all available space on the container, or the use of label space is for non-required information or other design-related elements (see 21 CFR 201.15(a)(3) through (a)(5) and 201.15(b)).

2. Text Size and Style

Sponsors should choose a font that is easy to read, not lightweight or condensed. A number of published references recommend a larger font size such as 12-point sans serif (e.g., Arial) to improve readability.[12,13] FDA recommends the use of at least a 12-point font whenever label size permits.

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[11] USP General Notices: 10. Preservation, Packaging, Storage, And Labeling;10.40.100; Expiration Date and Beyond-Use Date. USP has announced plans to relocate this information to General Chapter <7> *Labeling* in the near future.

[12] *Design for patient safety: A guide to the graphic design of medication packaging,* National Patient Safety Agency, Second Edition, 2007; *Design for patient safety: A guide to labeling and packaging of injectable medicines,* National Patient Safety Agency, Edition 1, 2008.

[13] Recommendations to the Safe Medication Use Expert Committee by the Health Literacy and Prescription Container Labeling Advisory Panel, May and November 2009, United States Pharmacopia (USP), posted April 2010.

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3. Contrast of Text and Background Color

The color contrast between the text and the container label background color should be chosen to afford adequate **legibility** of the text. Sponsors should avoid color combinations that do not afford maximum legibility of text (e.g., pale yellow text on white container label background).

Text that is raised or recessed (i.e., embossed or debossed) on clear, transparent, or translucent containers (e.g., LDPE vials) is generally illegible. For these types of container labels, we recommend individually overwrapping the product so that a legible label is applied to the overwrap, and the product should be retained in the overwrap until it is administered.

4. Information Crowding and Visual Clutter

When labels are crowded, text size and prominence are generally decreased, and important information may be difficult to read and/or easily overlooked. Lines or blocks of text should be separated by sufficient white space to avoid crowding or clutter. We recommend placing less important information on a side or back panel of the container label and carton labeling, rather than on the PDP, or placing it, as appropriate, in the prescribing information.

Apart from required information about a product's manufacturer, distributor or packer (see § 201.1), information about business partnerships should not appear on the label or labeling.

The use of logos, bars, stripes, watermark graphics, lines, and symbols is discouraged on container labels and/or carton labeling because they can distract the reader from important information and add to label clutter. When such items are included, the graphic design should not compete with, interrupt, or distort important information.

We recommend not superimposing text over images or logos or placing a logo immediately before or after the proprietary name, because the logo can often look like an additional letter in the proprietary name. In addition, there should be no intervening written, printed, or graphic matter between the proprietary name, established name, and product strength (see § 201.10(a)).

Images of tablets and/or capsules can help pharmacists or other healthcare providers confirm they are dispensing the correct medication when comparing the product to be dispensed against the product contained in the commercial container closure system. If an image is used on the PDP, the image should appear at the bottom of the label and should not compete in size or prominence with the proprietary and/or **nonproprietary name** and strength information. Images should represent the actual tablet or capsule and reflect the true size, color, and imprint. Schematic or computer-generated images should not be used.

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5. Dangerous Abbreviations, Acronyms, and Symbols

Certain abbreviations, acronyms, and symbols are dangerous and should not be used because they are frequently misinterpreted and can lead to mistakes that result in patient harm. For example, the abbreviation *µg* for microgram should not be used because it has been mistaken as *mg*, meaning milligram. The abbreviation *mcg* is an appropriate abbreviation for microgram. The abbreviation *IU* for international unit also should not be used because it has been confused for the intravenous route of administration. Mistakes can also result from the use of abbreviations, symbols, and dose designations whose meaning is non-standardized and/or unfamiliar to the healthcare professional or other target reader.[14] For these reasons, sponsors should avoid using error-prone abbreviations or symbols for product names, doses, and strength designations on container labels and carton labeling. We refer you to The Joint Commission's "Do Not Use" list, as well as the Institute for Safe Medication Practices (ISMP) List of Error-Prone Abbreviations, Symbols, and Dose Designations for a list of commonly confused abbreviations, symbols, and dose designations.[15,16,17]

E. Avoid Look-alike Container Labels and Carton Labeling

Look-alike container labels and carton labeling have frequently contributed to product selection errors leading to the dispensing and administration of the wrong drug, wrong strength and/or wrong dose. Sponsors should create a container label and carton labeling design that is sufficiently distinct from that of their other products and the products of other manufacturers so that the end user is able to correctly identify, select, dispense, and administer the appropriate medication, strength, and dose.

The potential for product confusion is especially problematic when products with similar looking container labels or carton labeling are customarily stored side-by-side or near one another. To reduce the risk of error, FDA recommends the following:

1. Corporate Trade Dress

Sponsors should avoid or minimize the use of **corporate trade dress** that could make it difficult for end users to distinguish between different medications or different strengths of the same medication.

[14] FDA/Institute for Safe Medication Practices Campaign to Eliminate Use of Error-Prone Abbreviations, http://www.ismp.org/tools/abbreviations/.
[15] The Joint Commission 2001; http://www.jointcommission.org/assets/1/18/Official_Do_Not_Use_List_6_111.PDF.
[16] The Institute for Safe Medication Practices' List of Error-Prone Abbreviations, Symbols, and Dose Designations, 2010, http://www.ismp.org/tools/errorproneabbreviations.pdf.
[17] USP General Chapters: <1265> Written Prescription Drug Information-Guidelines.

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2. Use of Color

A common feature of look-alike products is the use of the same or similar colors in the container labels and carton labeling of multiple products across a company's entire product line or within a line of related products. We recommend that sponsors use color prudently to bring attention to the product name, strength, and important warning(s). Sponsors also should bear in mind that (1) individuals can perceive colors differently and some individuals may be colorblind, (2) identification of products by color might replace reading the label, (3) there are a limited number of discernible colors available, and (4) colors can look different under certain lighting conditions. Accordingly, color should not be the only element used as a means to distinguish different container label and carton labeling of multiple products across a company's entire product line or within a line of related products.[18]

In response to medication errors associated with the use of color on pharmaceutical product container labels, carton labeling, and packaging, FDA held a public hearing on March 7, 2005, to discuss the pros and cons of each of the following applications of color.[19] Based on these discussions, FDA recommends the following:

a. Color Differentiation

Color differentiation is an effective tool that can (1) differentiate products within a manufacturer's product line; (2) differentiate strengths within a manufacturer's product line; and (3) highlight certain aspects of the label, such as important warning statements. When applying color, sponsors should ensure that the text highlighted by the color has adequate color contrast against the background color. Color differentiation is most effective when the color used has no association with a particular feature and there is no pattern in the application of the color scheme.

b. Color Coding

Color coding is a technique that uses color to designate a specific meaning. FDA generally recommends avoiding color coding in most instances. Color coding is reserved for special circumstances and only after human factors testing and feedback on the prototype from all end users is received and evaluated by FDA prior to use.

The use of color coding on drug labels has been limited and not without risk. Color coding schemes developed to decrease error may actually increase error when the color is relied upon as a shortcut to proper identification (i.e., not reading the label). Errors can also occur when the color code is not meaningful to end users outside the limited environment where the color coding has an established use (e.g., Broselow Tape in the emergency room, and user-applied, color-coded labels in the operating room).

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[18] Medication Errors, Second Edition, 2007, p. 119.

[19] See the *Federal Register* notice "Use of Color on Pharmaceutical Product Labels, Labeling, and Packaging; Public hearing," February 3, 2005 (70 FR 5687).

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Certain applications of color coding are appropriate. Examples include the color coding of certain drug product strengths such as warfarin, levothyroxine, and conjugated estrogen-containing products. The colors of the strengths are universally color coded across all manufacturers. Another example is color coding the caps used for ophthalmic products to distinguish a therapeutic class (e.g., beta-blockers have a yellow cap). Although color coding the caps is useful to ophthalmologists and some patients in identifying the therapeutic class of medication, it is generally not helpful to end users outside of ophthalmology. In fact, the color coding has made it difficult for these users to differentiate between drugs *within* the same therapeutic class when the color code was used on the container label and carton labeling. Because these products are typically stored near each other, the similar appearance of the container labels and carton labeling has led to dispensing and administering the wrong strength, wrong dose, and wrong product. For these reasons, the color coding of ophthalmic products is limited to the cap color.

IV. SPECIAL CONSIDERATIONS AND RECOMMENDATIONS

A. Proprietary, Established, and Proper Names

Sponsors should maximize the readability of proprietary, established, and proper names on the container label and carton labeling. We recommend capitalizing only the first letter in the proprietary name because words written in all-capital letters are less legible than words written in mixed case letters. Moreover, the established or proper name and proprietary name should be displayed in a manner consistent with the FDA regulations, taking into account all pertinent factors, including typography, layout, contrast, and other printing features (for drugs see 21 CFR 201.10(g)(2)); for biologic products see 21 CFR 610.62).

The established name for drug products should include the finished dosage form. If space does not permit the finished dosage form to appear on the same line as the active ingredient, we recommend placing the finished dosage form on the next line below the active ingredient.

Mydrug (drugozide injection)	or	Mydrug (drugozide) injection	or	Mydrug (drugozide) Injection

For biological products, the proper name for biological products should not include the finished dosage form. The finished dosage form can appear on the line below the proper name.

Mydrug (drugozide) Injection	drugozide Mydrug Injection

Mixed case or **tall man lettering** on approved container labels and carton labeling can sometimes be used to help distinguish similar looking, established name pairs that have been confused postmarket. Dissimilar letters in each of the established names are placed in upper case

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letters to bring attention to the point of dissimilarity between the names of concern (e.g., drugMY versus drug). We recommend that applicants consult FDA's medication error prevention staff before using this technique and supply data concerning the postmarket confusion concern, a description of how the letter string was selected, and data demonstrating that the proposed presentation will adequately distinguish between the potentially confusing product names. A list of approved name pairs that use mixed-case typography can be found on the FDA Web page at www.fda.gov/Drugs/DrugSafety/MedicationErrors/ucm164587.htm.

B. Product Strength

A product's strength or concentration is critically important information for the end user. If the product strength is not clearly displayed on the container label, or is expressed in units of measure that are incongruent with those used in the dosing instructions, the wrong strength can be selected or the wrong dose administered (i.e., over- or under-dosing). We recommend the following measures to avoid or minimize commonly reported dosing errors:

1. Strength Differentiation

Product selection errors leading to under- or over-dosing can occur when different strengths of the same product or similar strengths of different products are stored or displayed in close proximity. Sponsors should ensure that the product strength stands out on the container label and carton labeling. Appropriate techniques for this purpose include the use of boxing, a prominent typeface or type weight, and color differentiation, among others.

2. Strength Designation

Product strength designations should use a consistent unit of measure across all elements of the labeling (e.g., container, carton, and prescribing information). The product strength should match the units of measure described in the DOSAGE AND ADMINISTRATION section of the prescribing information to avoid error. For example, user confusion and dosing errors can occur if product strength is expressed on the label in percentage, but the directions for dosage and administration of the drug are expressed in milligrams. Sponsors also should use the same units of measure when labeling multiple products containing the same active ingredient (e.g., use *mg* for milligram to express the strength for all nitroglycerin products rather than using both mg and mcg).

3. Small Volume Parenteral Products

For small volume parenteral products, the product strength should be expressed as total quantity per total volume followed by the concentration per milliliter (mL), as described in the USP, General Chapter <1> *Injection*.[20] A number of overdoses have occurred with small-volume

[20] USP General Chapter: <1> Injections; Labels and Labeling; strength and total volume for single- and multiple-dose injectable drug products. USP has announced plans to relocate this information to General Chapter <7> *Labeling* in the near future.

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parenterals because of healthcare practitioner and patient failure to determine the total amount of drug in the container. In most cases, the user noticed the concentration (e.g., 10 mg/mL) but failed to see the net quantity (e.g., 10 mL), which often appears in a different location on the container label. This confusion has led to administration of the entire contents of the container, when only a portion of the total volume was needed.

To avoid such confusion, the strength per total volume should be the primary and prominent expression on the principal display panel of the label, followed in close proximity by strength per milliliter enclosed by parentheses. For example:

500 mg/10 mL
(50 mg/mL)

If the product contains a volume of less than 1 mL, the product should never be labeled with a concentration of mg/mL, since this may lead end users to mistakenly think the container has more drug in it than it actually does, which can lead to under-dosing. For containers holding a volume of less than 1 mL, the strength per fraction of a milliliter should be the only expression of strength. For example:

12.5 mg/0.625 mL
or
12.5 mg per 0.625 mL

4. Expression of Strength for Dry Powder Products

Dry powder products should express the strength in terms of the total amount of drug per vial as follows:

XX mg/vial or XX mg per vial

Instructions for reconstituting the product and the resultant concentration should be included on the vial, if space permits. These instructions will inform persons responsible for preparing the product what type and volume of diluent should be used for reconstitution, and the amount of drug contained in each milliliter once reconstituted. If space permits, information on the expiration date and post-reconstitution storage should also be included.

5. Salt Nomenclature

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When a product contains an active ingredient that is a salt, the USP Salt Policy should be applied when naming and labeling drug products.[21]

6. Prodrugs

For **prodrugs**, the product strength should be expressed in terms of the established or proper name of the prodrug — for example, Valtrex (valacyclovir hydrochloride tablets) is a prodrug for acyclovir. After oral administration, valacyclovir hydrochloride is rapidly absorbed from the gastrointestinal tract and nearly completely converted to acyclovir. Therefore, the strength of this product is based on valacyclovir rather than acyclovir.

7. Metric Measurements

The dose or expression of strength should appear in metric units of measure such as mL, mg, and mcg, rather than apothecary or household measurements (e.g., tsp for teaspoon, TBSP for tablespoon, drams, and grains) or ratios (e.g., 1:1000).

Fatal errors have occurred when healthcare providers or patients miscalculated medication doses when converting from one unit of measure to another (for example, the usual dose is expressed in terms of a milligram unit of measure, but the product strength is expressed as a ratio, requiring conversion of the ratio to a milligram dose).

8. Location of Net Quantity Statements

Product selection or dosing errors can occur if the net quantity statement is mistaken for the product strength, leading to under- or over-dosing. This error generally occurs when the product strength overlaps with the product net quantity (e.g., 100 tablets versus 100 mg) or when the net quantity is presented more prominently on the label than is the product strength. The net quantity statement should appear on the PDP but should be separate from and less prominent than the statement of strength (e.g., not highlighted, boxed, or bolded).

9. Leading and Terminal Zeros, Decimals, and Commas

Numbers containing decimal points in the declaration of strength can lead to tenfold dosing errors when the decimal point goes unseen (e.g., 4.0 mg is seen as 40 mg, or .4 mg is read as 4 mg). To minimize such errors, the quantity of active ingredient in the statement of strength should be presented in whole numbers, and not with a decimal point that is followed by a terminal zero (e.g., 4 mg, not 4.0 mg). Conversely, decimal numbers smaller than one should always be preceded by a zero (e.g., 0.4 mg, not .4 mg). This serves to enhance the visibility of the decimal point.

[21] USP General Chapters <1121> Nomenclature; Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Preparations.

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Commas should be used for numbers 1,000 and above to improve the legibility of larger numerals.

C. Route(s) of Administration

The route of administration should be described without abbreviation. We recommend using positive statements such as "for intravenous use," "give by subcutaneous injection," or "topical use only." Negative statements such as "NOT for intrathecal use" should not be used because it is easy to overlook the word "not," even when it is emphasized by bolding, underlining, or other means. Using affirmative statements will help to ensure that end users understand the intended route of administration, even if they do not read every word.[22,23,24]

D. Warnings for Critical Information

When warning statements are added to the container label or carton labeling, they should be written affirmatively. Non-affirmative warning statements have been confused. For example, the warning "Not for intrathecal use" has been confused as "For intrathecal use." Affirmative statements such as "For Intravenous Use Only," "Fatal if given by any other route," or "Must Dilute Before Use" are more easily understood.

E. Expiration Dates

Currently, manufacturers use various ways to express the expiration date on a product label. Some express the expiration date with the month and day, while others use the month and year. Most use abbreviations to express these dates (e.g., MA12). The use of abbreviations for expiration dates has led to confusion, misinterpretation, and sometimes delays in treatment because the abbreviation was interpreted incorrectly. For example: "MA" could mean March or May, whereas the number 12 could represent the day, month, or year. Accordingly, FDA recommends the expiration date be expressed in a standard format, using three-letter text for the month, two-digit numerals for the day (if included), and four-digit numerals for the year, as shown below:

MMMYYYY (e.g., JAN2013)

or

MMMDDYYYY (e.g., JAN012013)

F. Bar Codes

[22] Eastman Kodak Company. Ergonomic Design for People at Work, Second Edition. Chengalur SN, et al., eds. Hoboken, NJ: John Wiley & Sons, 2004.
[23] Handbook of Warnings. Wogalter MS, ed. Mahwah, NJ: Lawrence Erlbaum Associates, 2006.
[24] Proctor RW, Vu KL. Handbook of Human Factors in Web Design. United Kingdom: Routledge, 2005.

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A bar code should be placed on the immediate container label and carton labeling of most drug products. The barcode should be surrounded by enough white space to allow scanners to read the bar code properly (see 21 CFR 201.25(c)(2)). Print density should be consistent to allow for an accurate scan. The bar code should be placed in a conspicuous location (e.g., not on the bottom of a carton) where it will not be difficult to read because of distorted text. Additionally, the barcode should be placed in an area where it will not be damaged because it appears at the point of label separation (e.g., perforation).

G. National Drug Code Numbers

Each listed drug product[25,26] is assigned a unique 10-digit, 3-segment number known as the national drug code (NDC). The NDC number identifies the labeler, product, and commercial package size.[27,28] When selecting the product code for NDC numbers of drug products with multiple strengths, FDA recommends the following:

Avoid assigning product codes that are numerically similar or identical. The similarity of the product code numbers has led to selecting and dispensing of the wrong strength and wrong drug. The middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Therefore, assignment of sequential numbers for the middle digits is not an effective differentiating feature (e.g., 6666, 6667, and 6668), nor is using the identical product code for injectable products containing the same concentration of drug but different total volumes. For example, injectable products might contain the same product concentration but contain a different total amount of drug in the container because of differences in the fill volume (e.g., 20 mg/2 mL (10 mg/mL), 40 mg/4 mL (10 mg/mL)). When the same product code number is used for all of the different containers, healthcare practitioners have had difficulty distinguishing the difference in total drug content. Each of these injectable products should therefore have a different product code assigned. Another example is when injectable products contain the same concentration and same total drug content but delivers different volumes or doses. For example, a drug might be marketed in two prefilled pen devices, each containing a 10 mg/mL solution, and total volume of 3 mL. However, one device might deliver dosages of 5 mg (0.5 mL) and the other might deliver dosages of 10 mg (1 mL). Each of these prefilled pens should be assigned a different product code to help avoid confusion between the two products.

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[25] Under section 510 of the Federal Food, Drug and Cosmetic Act (FD&C Act) (21 U.S.C. 360), as amended, and part 207 of FDA's regulations, with some limited exceptions, firms that manufacture, prepare, propagate, compound, or process drugs in the United States or drugs that are offered for import into the United States must be registered with the FDA (see 21 U.S.C. 360(b), (c), (d), and (i)). Every person who registers must, at the time of initial registration, list all drugs manufactured, prepared, propagated, compounded, or processed for commercial distribution (21 U.S.C. 360(j)(1)) (see also 21 CFR 207.20). Drug listing information must be updated in June and December each year. These updates must include drugs not previously listed (if any), and certain changes to information for previously listed drugs (21 U.S.C. 360(j)(2); 21 CFR 207.21(b) and 207.30).

[26] Information regarding FDA's Drug Registration and Listing is available on FDA's Web site at http://www fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/DrugRegistrationandListing/default htm.

[27] See 21 CFR 207.35(b)(3) for specific format requirements.

[28] Information regarding FDA's NDC Directory is available on FDA's Web site at http://www fda.gov/Drugs/InformationOnDrugs/ucm142438 htm.

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If for some reason the middle digits cannot be revised, increase the prominence of the middle digits by increasing their size in comparison to the remaining digits in the NDC number or put them in bold type. For example: xxxx-XXXX-xx.

Avoid the reuse of NDC numbers. The reuse of NDC numbers has led to the dispensing and administration of the wrong drug or wrong strength.

H. Controlled Substance Schedule

Each commercial container of a controlled substance must prominently display the controlled substance schedule (i.e., CII through CV) as described in 21 CFR 1302.03 and 1302.04. The controlled substance schedule and the proprietary or established name should be separated by white space, not directly juxtaposed. For injectable drugs that are classified as Schedule IV controlled substances, FDA recommends the designation "CIV" rather than "C-IV." This is because "-IV" can be misread as an abbreviation for intravenous, leading to administration of the product by the wrong route, or as a number, leading to misinterpretation of the product strength as 4 mg.

V. OTHER SPECIAL CONTAINER LABEL AND CARTON LABELING CONSIDERATIONS

A. Unit Dose Blister Pack Presentations

Various configurations are available for products packaged in blister packs. For example, they can be a strip of individual blister cells (unit doses) or they can be a sheet containing multiple tablets for a particular duration of therapy (e.g., 3 days, 5 days, monthly). The size of a unit-dose blister is generally small, and blisters are often torn apart, punctured, or removed from the outer carton by the end user. Therefore, FDA recommends the following when developing the container label and carton labeling for these packs:

1. Blister Cell Label

Ideally, the proprietary and established name, strength, lot number, expiration date, bar code, and manufacturer should appear over ***each*** blister cell so that this important information remains available to the end user up to the point at which the last dose is removed. Each blister should include only one dosage unit per blister (e.g., one tablet, one capsule).

In certain cases it may not be possible to design the packaging to accommodate all critical information on each blister cell. In such circumstances, a random display of the information can appear multiple times across the back of the blister or the important information should be displayed in such a manner that it is not destroyed or eliminated when dosage units are removed.

2. Product Strength

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The product strength on the principal display panel and other panels of the blister carton labeling should describe the milligram amount of drug per single unit (e.g., tablet, capsule) so that there is no confusion as to how much product is contained in a single unit as compared to the total contents of the entire blister card. We recommend the following:

XX mg per tablet or XX mg per capsule

3. Blister Cell Label Material and Readability

Color, type size, and font style should be carefully chosen based on the material used for the blister cell backing. Because the legibility of text printed on foil might be impaired due to the reflective nature of the material, it is important to ensure that information printed on foil is readily legible. When possible, a non-reflective material should be used to enhance readability of product information.

4. Blister Pack Label Design

Careful consideration should be given to the overall design of a blister pack label so that it does not lead to confusion and error. Sponsors should limit the number and variety of blister packs, and ensure that the packaging configuration makes sense for the dosage and administration of the drug product and the intended patient population. Although special packaging for specific treatment regimens might improve patient compliance and minimize the risk of accidental exposures to the drug, they can also be confusing and prone to dosing errors if not designed properly. Blister labeling design factors that have been associated with reported medication errors include, but are not limited to, the following:

- Presenting and sequencing doses in ways that do not match the product's approved usual dosage, leading to administration of the wrong dose. For example, the blister labeling presents the product or labels the product in a manner that provides for a fixed dose (e.g., twice-a-day dose) but the approved usual dosing regimen is variable (e.g., once or twice daily).

- Labeling doses in the package with days of the week when the dosage and administration does not require such sequencing. For example, a packaging configuration labeled with the days of the week (e.g., Mon., Tues., and Wed.) can lead to delays in starting therapy because patients wait to start their medication on the first specified day.

- Numbering each blister cell in sequence, such as controlled substances packaged in a 30-tablet blister pack and numbered from 1 to 30. Although this may be convenient for record keeping of controlled substances in facilities, the number has been confused for the tablet strength.

- Providing more doses than needed for a single course of treatment, leading to excessive duration of therapy (e.g., a 20-tablet pack for a product that should be administered once daily for a total of 5 days).

B. Labeling of Ferrules and Cap Overseals

Vials for injectable drug products often include elastomeric closures (stoppers), which are connected to the vials by bands, or *ferrules*. A cap overseal is a disc over a ferrule that protects the stopper. The ferrule and cap should be prominently visible on the vial immediately before administering the drug product. Given their location, the information provided on ferrules and caps of medication vials has a critical role in providing crucial information to the healthcare provider and should be limited to important safety messages critical for the prevention of imminent, life-threatening situations. If no cautionary statement is necessary, the top surface of the vial, including the ferrule and cap overseal, should remain blank. Other statements (e.g., lot numbers) can appear on the side of the ferrule but should not detract from any cautionary statement appearing on the top surface.

The USP created a Labeling on Ferrules and Cap Overseals section of General Chapter <1> *Injections*, which will become official on December 1, 2013. Applicants and sponsors should comply with the recommendations set forth in the revised USP General Chapter <1>.[29]

C. Color Closure System for Concentrated Potassium Chloride

The use of a black closure system on a vial (e.g., a black flip-off button and a black ferrule to hold the elastomeric closure), or the use of a black band or series of bands above the constriction on an ampule, is used only for Potassium Chloride for Injection Concentrate. This unique color closure system differentiates this concentrated strength of potassium chloride from other less concentrated strengths of potassium chloride and alerts the end user that the product is more concentrated.[30] As such, a black cap/ferrule/lines should not be used on any other drug product.

D. Labels for Large Volume Parenterals

FDA receives many reports of confusion and errors involving large-volume parenteral products. These reports cite similarity of the containers, lack of prominence of important information on the label, and label clutter. These concerns were addressed at a joint public meeting held by FDA, ISMP, and USP in 2007.[31] Based on the information and recommendations presented at the public meeting, FDA considers the following information to be essential for the container label of large volume parenterals:

- Name and strength
- Statement "Do not add supplementary …to the Y port…"
- Statement "Sterile"

[29] USP General Chapters; General Test and Assays <1> Injections; Packaging Containers for Injections. USP has announced plans to relocate this information to General Chapter <7> *Labeling* in the near future.
[30] USP General Chapters; General Test and Assays <1> Injections; Packaging Containers for Injections. USP has announced plans to relocate this information to General Chapter <7> *Labeling* in the near future.
[31] See the *Federal Register* notice "Improving Patient Safety by Enhancing the Container Labeling for Parenteral Infusion Drug Products; Public Meeting," November 28, 2006 (71 FR 68819).

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- Statement "Each 100 mL contains….."
- General and/or Special Storage Requirements such as:
    - "See USP Controlled Room Temperature"
    - "Protect from Freezing" should only be used if the drug product is adversely affected by freezing[32]
- Labels of Ports (e.g., arrows with "med" or "set")
- Barcode
- Lot number and Expiration Date
- Recycling code symbol
- Statement "For use only with a calibrated infusion device"
- Revision date
- "See prescribing information" (not "see package insert")
- "Additive compatibility, consult pharmacist" (not "Compatibility of additives, check with a pharmacist")

The following information is considered label clutter and should not be included on the large volume parenteral container label or presented, as appropriate, in the prescribing information:

- All secondary trademark information (e.g., "VisIV", "Intravia" Container)
- Symbols (e.g., circles that represent strength) should not be included on the container label or in the prescribing information
- Statements such as "Caution – check for minute leaks by squeezing container firmly…" and "If leaks are found…"
- Statement "Use only if solution is clear and container is undamaged"
- Statements about "series connection" should not be included on the container label or in the prescribing information
- Osmolarity statement
- Lactic acidosis statement (e.g., on lactated ringers bags)
- Statements such as "printed in USA"
- Manufacturer full address
- Statements such as "Dose intravenously as directed by physician" should not be included on the container label or in the prescribing information
- Statement "Whenever possible use central route"
- pH statement
- Blood transfusion warning
- Statements such as "non-pyrogenic"
- Warnings for purposes of interstate commerce should not be included on the container label or in the prescribing information

[32] USP General Notices: *10.30.90. Protection From Freezing.* USP has announced plans to relocate this information to General Chapter <7> *Labeling* in the near future.

Reference ID: 3356818

E. Transferable or Peel-Off Labels for Injectable Medications

Currently, once an injectable medication is withdrawn from the commercial container closure (e.g., vial or ampule) into a syringe for administration, the syringe no longer provides information needed by the end user to verify the drug name and strength prior to administration. Such unlabeled medication has led to administration of the wrong drug and wrong strength.

FDA recommends that sponsors develop, when possible, a transferable or peel-off label for the commercial container of injectable products. This type of label can help to minimize the use of unlabeled syringes because the label would be attached to the commercial container closure, present at the point of product preparation, and not be discarded as in the case with other auxiliary labels often provided with the carton.

F. Double-sided Labels and Labeling

Printing information on both the front and back panels of labels and labeling can be an effective way to present safety information and, if done correctly, can help prevent medication errors. When double-sided printing is used on clear, transparent, or translucent labels and labeling, such as LDPE vials or intravenous bags, the text should be readable in both the upright and inverted positions and should not overlap with other text.

G. Pharmacy Bulk Packages

For Pharmacy Bulk Packages (PBPs), a prominent, boxed declaration reading “Pharmacy Bulk Package – Not for Direct Infusion” should be placed on the principal display panel following the expression of strength. This statement can be made more prominent by using boldface type, large size type, or a contrasting color. The container label for PBPs should not include graduation marks.

H. Communication of Important Product Changes

Changes to marketed products such as new strengths or concentrations, or changes in formulation, or changes in certain inactive ingredients should be communicated to health practitioners on the container label, if space permits, and on the carton labeling. For example, a change in product strength should be communicated as “New Strength” or “Note New Strength.” This statement should appear on the principal display panel for a period of 6 months.

I. Dosing Devices

Dosing devices included with a drug product should be appropriate for the dosages to be measured.[33] The dosing device should deliver an oral solution in a volumetric unit of measure,

[33] See the FDA guidance for industry *Dosage Delivery Devices for Orally Ingested OTC Liquid Drug Products* addresses issues concerning dosing devices for OTC liquid drug products (available at http://www fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default htm.

Reference ID: 3356818

preferably milliliters (mL), consistent with recommended dosing. For example, sponsors should not create an oral syringe that is calibrated in milligrams rather than milliliters.

J. Product Samples

Each product sample unit must bear a label that clearly denotes its status as a drug sample (e.g., "sample," "not for sale," "professional courtesy package" (21 CFR 203.38(c)). At a minimum, product sample labels must also include the proprietary and nonproprietary names; product strength; lot number; and the name of the manufacturer, packer, or distributor of the drug (21 CFR 201.10(i)). We also strongly encourage including the expiration date and NDC number. Professional samples packaged as packs or kits should not be labeled with terms such as *starter*, *starter samples*, and *patient starter pack*.[34] In addition, the sponsor should consider providing a blank open space on the label so the provider of the drug sample can write or affix a label with the patient name and specific instructions for use.

K. Package Type

Including the **package type** on container labels and carton labeling (e.g., single-dose and pharmacy bulk packages) is important in situations where it is unclear how the medication should be safely handled and used simply by viewing the container. For example, vials containing a specific quantity of a drug product intended to be used as a single dose on a single patient should include the term single dose on the vial to differentiate them from multiple-dose vials and alert the user to the appropriate use of the product.

In addition, when the product appears to be in a child-resistant container (e.g., unit-dose blister) but the container is NOT in fact child-resistant, it is important to include a statement on the label indicating the package is not child-resistant. For example, "This package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be used."

USP General Chapter <659> *Packaging and Storage Requirements* includes package-type terms and definitions.

L. Quick Response Code

A Quick Response Code (QR code) is a type of matrix bar code (or two-dimensional bar code) that can be read by a mobile phone. QR codes may provide various bits of information (e.g., Internet address, phone numbers). FDA has not developed a formal position on the use of QR Codes. If a manufacturer uses a QR code, we recommend that it appear on the side or back panel of the container label or carton labeling, away from the bar code and in a size that does not compete with, distract from the presentation of other required or recommended information on the label.

[34] See the final rule "Prescription Drug Marketing Act of 1987; Prescription Drug Amendments of 1992; Policies, Requirements, and Administrative Policies" (December 3, 1999, 64 FR 67720 at 67742), available at http://www.gpo.gov/fdsys/pkg/FR-1999-12-03/pdf/99-30954.pdf.

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GLOSSARY

Container Closure System: A *container closure system* refers to the sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product. A *packaging system* is equivalent to a container closure system.

Corporate Trade Dress: As used in this guidance *corporate trade dress* means the manner in which a company packages, wraps, and labels, a drug or biologic product including the use of color schemes, sizes, designs, shapes, and placements of words or graphics on a container label and/or carton labeling.

End user: *End users* include, but are not limited to, the patient, patient's caregiver, the prescribing physician, nurse, pharmacist, pharmacy technician, and other individuals who are involved in routine procurement, stocking, storage, and administration of medications (e.g., medication technicians).

Established Name: Section 502(e)(3) of the FD&C Act (21 U.S.C. 352) states that "the term 'established name,' with respect to a drug or ingredient thereof, means (A) the applicable official name designated pursuant to section 508 [(21U.S.C. 358)], or (B) if there is no such name and such drug, or such ingredient, is an article recognized in an **official compendium** [see definition below], then the official title thereof in such compendium, or (C) if neither clause (A) or clause (B) of this subparagraph applies, then the common or usual name, if any of such drug or such ingredient, except that where clause (B) of this subparagraph applies to an article recognized in the United States Pharmacopeia and in the Homeopathic Pharmacopeia under different official titles, the official title used in the United States Pharmacopeia shall apply unless it is labeled and offered for sale as a homeopathic drug, in which case the official title used in the Homeopathic Pharmacopeia shall apply."

Label: As defined in section 201(k) of the FD&C Act (21 U.S.C. 321(k), the term *label* means a display of written, printed, or graphic matter upon the immediate container of any article, or is easily legible through the outside container or wrapper.

Labeling: As defined in section 201(m) of the FD&C Act, the term *labeling* means "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article."

Legibility: *Legibility* is concerned with how easy it is to distinguish individual letters. Legibility is dependent on the typeface design.

Official Drug Product: USP General Notices, Section 2.20, Official Articles defines an *official product* as a drug product, dietary supplement, compounded preparation, or finished device for which a monograph is provided.

Reference ID: 3356818

Official Compendium: Defined in section 201(j) of the Act as "the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, official National Formulary, or any supplement to any of them."

Package Type: For the purposes of this guidance, the *package type* is a description of the container-closure system that drug substances and final drug dosage forms are contained in.

Packaging: A *package* or *market package* refers to the container closure system and labeling, associated components (e.g., dosing cups, droppers, spoons), and external packaging (e.g., cartons or shrink wrap). A market package is the article provided to a pharmacist or retail customer upon purchase and does not include packaging used solely for the purpose of shipping such articles.

Principal Display Panel: The term *principal display panel* refers to the part of a label that is most likely to be displayed, presented, shown, or examined under customary conditions of display on the pharmacy or retail shelf.

Prodrugs: *Prodrugs* are products that are converted to another active moiety once ingested.

Proper name: For biological products, the *proper name* means the name designated in the license for use upon each package of the product (21 CFR 600.3(k)).

Proprietary Name: The exclusive name of a drug substance or drug product owned by a company under trademark law regardless of registration status with the Patent and Trademark Office.

Readability: *Readability* refers to the ease with which a reader can scan over paragraphs of type. Readability is dependent on the manipulation or handling of the type. A highly legible typeface can be made unreadable by poor typographic design. Factors that affect readability include: line lengths, point size, leading, typeface selection, spacing, type alignment, and background.

Tall Man Lettering: *Tall man lettering* involves highlighting the dissimilar letters in two names to aid in distinguishing between the two.[35]

[35] Institute of Safe Medication Practices, http://www.ismp.org/faq.asp#Question_8.

Reference ID: 3356818

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/s/

TYREE L NEWMAN
08/13/2013

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # Product Name: NDA 202317 / Valchlor (mechlorethamine) gel 0.016%.

PMR Description: An assessment and analysis of spontaneous reports of inadvertent exposure of anyone other than the patient who has been exposed to Valchlor (Mechlorethamine Hydrochloride) Gel 0.016%. Specialized follow-up should be obtained on these cases to collect additional information on the events. Continue the enhanced pharmacovigilance for a period of 2 years from the date of approval.

PMR Schedule Milestones:		
	Final Protocol Submission:	10/31/13
	Study Completion:	10/31/15
	Final Report Submission:	12/31/15

1. During application review, explain why this issue is appropriate for a PMR instead of a pre-approval requirement. Check type below and describe.

   ☐ Unmet need
   ☐ Life-threatening condition
   ☒ Long-term data needed
   ☒ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☒ Small subpopulation affected
   ☐ Theoretical concern
   ☐ Other

   Knowledge of actual experience in clinical use is needed to inform safety further.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Reference ID: 3356206

Inadvertent exposure of others is an uncertain safety hazard during use of this topical chemotherapy intended for home use.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☒ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☒ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Reference ID: 3356206

- Expedited reports of both serious and non-serious outcomes for all initial and follow-up adverse drug experiences resulting from secondary exposure to the skin, mucous membranes, and eyes of individuals other than the patients being treated submitted as Postmarketing 15-day "Alert Reports";
- A summary and line listing of all secondary exposure events from postmarketing sources, including consumer reports, solicited reports, and foreign reports submitted in each PADER/PBRER; and
- Documentation of attempts to contact all reporters of events, and obtain findings about the events, including but not limited to the circumstances leading to the exposure, ultimate highest severity of the exposure, and resolution status.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

Reference ID: 3356206

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

---

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_RCK_____
(signature line for BLAs)

Reference ID: 3356206

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/s/

TYREE L NEWMAN
08/12/2013

ROBERT C KANE
08/12/2013

Newman, Tyree

From: Newman, Tyree
Sent: Thursday, August 08, 2013 4:29 PM
To: 'lisa wittmer'
Subject: NDA 202317: Tube labels and Carton advice

Good afternoon Lisa, in response to your August 2, 2013, email response regarding how the logo will be presented on the tube, carton and container labeling, the review team has proposed the following comments:

1. We strongly recommend (b) (4)

2. We prefer the Applicant revise the proprietary name to title case. The asymmetrical appearance of the letters helps to increase the readability of the proprietary name.

Please inform me if you have any questions. Please formally submit your proposed updates to your NDA.

Kind regards,

Tyree

Tyree Newman
Sr. Regulatory Health Project Manager
Food and Drug Administration
Office of New Drugs
Immediate Office
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Reference ID: 3354929

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/s/

TYREE L NEWMAN
08/08/2013

Newman, Tyree

From: Newman, Tyree
Sent: Tuesday, August 06, 2013 1:06 PM
To: 'lisa wittmer'
Subject: NDA 202317 - Labeling response advice

Good afternoon Lisa, please see the attached revised package insert and medication guide for NDA 202317 in tracked changes for your review.

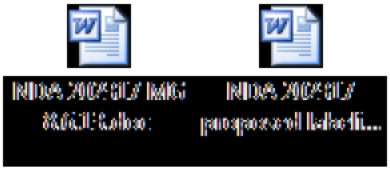
Please review the FDA's edits/comments and, using the same draft, do the following:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you do not agree with the labeling revisions, provide your comments and proposed language (shown in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

In addition, please review the document for formatting.

Please submit the revised package insert and medication guide on or before August 9, 2013.

Please confirm receipt of this e-mail. If you have any questions, feel free to contact me.



Kind regards,

Tyree

Tyree Newman
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15 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

TYREE L NEWMAN
08/06/2013

Newman, Tyree

From: Newman, Tyree
Sent: Friday, August 02, 2013 9:31 AM
To: lwittmer@ceptaris.com
Subject: NDA 202317 - Revised proposed PMR

Good morning Lisa, please see below the revised proposed PMR regarding NDA 202317 for your review, if you are in agreement, we ask you to submit both by email and officially a copy of the PMR to us with a statement that you agree to perform the trial as described and within the timelines that you specified for the trial. Please confirm agreement with the following proposed wording:

PMR Description: An assessment and analysis of spontaneous reports of inadvertent exposure of anyone other than the patient who has been exposed to Valchlor (Mechlorethamine Hydrochloride) Gel 0.016%. Specialized follow-up should be obtained on these cases to collect additional information on the events. This **enhanced pharmacovigilance** should continue for a period of 2 years from the date of approval. The following components should be assessed and analyzed in a final report:

- Expedited reports of both serious and non-serious outcomes for all initial and follow-up adverse drug experiences resulting from secondary exposure to the skin, mucous membranes, and eyes of individuals other than the patients being treated submitted as Postmarketing 15-day "Alert Reports";
- A summary and line listing of all secondary exposure events from postmarketing sources, including consumer reports, solicited reports, and foreign reports submitted in each PADER/PBRER; and
- Documentation of attempts to contact all reporters of events, and obtain findings about the events, including but not limited to - the circumstances leading to the exposure, ultimate highest severity of the exposure, and resolution status.

Submit the protocol for FDA review and concurrence before commencing the process and before the "Final protocol date below"

PMR Schedule Milestones:

Final Protocol / Plan Submission:	10/2013
Study Completion:	10/2015
Final Report Submission:	12/2015

Kind regards,

Tyree

Tyree Newman

Reference ID: 3351404

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Reference ID: 3351404

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/s/

TYREE L NEWMAN
08/02/2013

Newman, Tyree

From: Newman, Tyree
Sent: Thursday, July 18, 2013 5:02 PM
To: lisa wittmer
Subject: NDA 202317 (Valchlor) - Proposed PMR

Good afternoon Lisa, as we continue our review of your application (NDA 202317, Valchlor), our normal policy is to consider labeling and post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the following study is necessary as a post-marketing requirements (PMR), based on the data available to date. These brief descriptions of the necessary study, attached, are intended to describe the main objectives/characteristics of interest. Please provide edits and comments in clarifying and specifying mutually acceptable descriptions of the key elements needed to fulfill the objective. We are available to discuss by tcon, if needed. Submit the protocol/plan of investigation for FDA review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you submit a complete protocol that has already received full concurrence by FDA.

Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Note that milestone dates only need month and year. For milestone calculation purposes only, assume that an approval occurs on the PDUFA date. Please confirm agreement with the wording and/or provide edits in track changes [in WORD] along with the proposed milestone:

Perform and report enhanced pharmacovigilence (PV) for Valchlor for 2 years following introduction into the U.S. market, to assess risks related to inadvertent exposure of anyone other than the patient to Valchlor, by the following additions to routine PV:

- Submit expedited reporting of both serious and non-serious outcomes for all initial and follow-up adverse drug experiences as Post marketing 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 each PADER/PBRER.
- Document your attempts to contact all reporters of events, and findings of the events, including but not limited to - identify circumstances leading to the exposure, ultimate highest severity of the exposure, and resolution status.

PMR Schedule Milestones:

Final Protocol / Plan Submission:	MM/YYYY
Study Completion:	MM/YYYY
Final Report Submission:	MM/YYYY

Please submit the protocol for FDA review and concurrence before commencing the process and before the “Final protocol date below.

Lastly, please provide your response to this proposal by 7/24/13.

Kind regards,

Tyree

Tyree Newman
Sr. Regulatory Health Project Manager
Food and Drug Administration
Office of New Drugs

Reference ID: 3346097

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/s/

TYREE L NEWMAN
07/24/2013

Newman, Tyree

From: Newman, Tyree
Sent: Monday, July 22, 2013 5:30 PM
To: 'lwittmer@ceptaris.com'
Subject: NDA 202317 - Carton and container labeling advice

Good afternoon Lisa, please see the following comments in response to the carton and container labeling regarding NDA 202317:

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)
4. (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.

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.

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).

Please provide a response by July 29, 2013.

Reference ID: 3345854

Kind regards,

Tyree

Tyree Newman
Sr. Regulatory Health Project Manager
Food and Drug Administration
Office of New Drugs
Immediate Office
Therapeutics Biologics and Biosimilars Team
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Silver Spring, MD 20993
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Reference ID: 3345854

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/s/

TYREE L NEWMAN
07/23/2013

MEMORANDUM OF TELECONFERENCE

Date: July 15, 2013

Subject: NDA 202317 (Valchlor) – PMC/PMR preliminary discussions

FDA Attendees (Agency):

Edvardas Kaminskas, M.D., Deputy Director (DHP)
R. Angelo De Claro, M.D., Medical Officer (DHP)
Nicole Verdun, M.D., Medical Officer (DHP)
Diane Leaman, Safety Regulatory Project Manager (DHP)
Afrouz Nayernama, , Pharm.D., Safety Evaluator (DPV)
Peter Waldron, M.D., Medical Officer (DPV)
Robert Kane, M.D., Deputy Director, Safety (DHP)
Tyree Newman, Regulatory Project Manager (DHP)

Ceptaris Therapeutics (Sponsor):

Lisa Wittmer, PhD – Vice President, Global Regulatory Affairs
Tim Henkel, MD - Executive Vice President, Head of Research and Development
Jeff Wilkins, MD - Chief Medical Officer
Robert Pullen, PhD - CMC Consultant
Dale Bennyhoff - Senior Quality Manager
Cathie Leister - Statistical Consultant
Jeff Shaver, PhD - Vice President, Project Management
Kelly Copeland - Vice President, Product Strategy

Background:

On July 15, 2013, the Agency requested and held a teleconference with Ceptaris Therapeutics to discuss potential PMC(s)/PMR(s) for NDA 202317. The purpose of the call was to inform Ceptaris of the pharmacovigilance PMC they can expect in the near future and the logistical process of how we intend to reach agreement on the proposed PMC(s)/PMR(s) and finalize the P.I.

Discussion Items:

- The Agency explained the purpose and logistical process of what Ceptaris can expect when they receive the initial proposed wording from the Agency for a pharmacovigilance PMC in the event an approval action is taken for NDA 202317.
    - The pharmacovigilance (PV) PMC will address the following:
        - 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.
- The Agency explained that Ceptaris will receive proposed wording from the Agency regarding the PMC objective and then the Agency and Ceptaris will work together on finalizing the PMC wording and agreeing on an adequate timeline of when the Agency can expect to receive the protocol or plan of conduct that Ceptaris will use to accomplish the PMC for the PV.
- The Agency stated additional PMC(s)/PMR(s) may be recommended depending on ongoing review of the application.
- Ceptaris inquired about the status of the REMS that was included in their submission. The Agency confirmed that a REMs would not be required.

Action Items:

- The Agency will forward the proposed PMC language to Ceptaris to review and provide feedback.

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/s/

TYREE L NEWMAN
07/22/2013

Newman, Tyree

From: Newman, Tyree
Sent: Wednesday, July 03, 2013 2:11 PM
To: 'lisa wittmer'
Subject: RE: NDA 202317

Good afternoon Lisa, in response to your July 1, 2013, request for clarification to a comment noted in the package insert for NDA 202317. The review team provided the following response for your reference:

Time to response analysis should be based on 71 responders (not the total 119 patients) in the Valchlor arm and 59 responders (not the total 123 patients) in the control arm.

Please inform me if you have any additional questions.

Kind regards,

Tyree

Tyree Newman
Sr. Regulatory Health Project Manager
Food and Drug Administration
Office of New Drugs
Immediate Office
Therapeutics Biologics and Biosimilars Team
10903 New Hampshire Ave.
Silver Spring, MD 20993
301-796-3907 (phone)
Tyree.Newman@fda.hhs.gov

From: lisa wittmer [mailto:lwittmer@ceptaris.com]
Sent: Monday, July 01, 2013 11:37 AM
To: Newman, Tyree
Subject: RE: NDA 202317

Tyree,
Ceptaris recognizes FDA's suggestion that text be included in the labeling (b) (4) to describe the time to response. However, there is an additional comment that we do not fully understand, specifically:

"Do not include non-responders in the time to response analysis"

Will FDA provide further explanation of the comment above shown in quotes and their preferred methodology (b) (4) of time to response?
Thanks,
Lisa

From: Newman, Tyree [mailto:Tyree.Newman@fda.hhs.gov]

Sent: Monday, July 01, 2013 11:14 AM
To: lisa wittmer
Subject: NDA 202317

Good morning Lisa, I received your voicemail regarding a question about comments made to the NDA 202317 package insert. Please email your question, and I will forward to the appropriate discipline to provide clarification.

Kind regards,

Tyree

Tyree Newman
Sr. Regulatory Health Project Manager
Food and Drug Administration
Office of New Drugs
Immediate Office
Therapeutics Biologics and Biosimilars Team
10903 New Hampshire Ave.
Silver Spring, MD 20993
301-796-3907 (phone)
Tyree.Newman@fda.hhs.gov

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/s/

TYREE L NEWMAN
07/03/2013

Newman, Tyree

From: Newman, Tyree
Sent: Thursday, June 27, 2013 12:52 PM
To: 'lisa wittmer'
Subject: NDA 202317 - Labeling response advice

Attachments: NDA 202317 proposed labeling 6.27.13.doc; xae.xpt; NDA 202317 MG 6.27.13.doc

Good afternoon Lisa, please see the attached package insert (with dataset) and medication guide for NDA 202317 in tracked changes for your review.

Please review the FDA's changes/comments and, using the same draft, do the following:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you do not agree with the labeling revisions, provide your comments and proposed language (shown in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

In addition, please review the document for formatting.

Please submit the revised package insert and medication guide on or before July 8, 2013.

Please confirm receipt of this e-mail. If you have any questions, feel free to contact me.

NDA 202317 proposed labeling 6. | xae.xpt (939 KB) | NDA 202317 MG 6.27.13.doc (100...

Kind regards,

Tyree

Tyree Newman
Sr. Regulatory Health Project Manager
Food and Drug Administration
Office of New Drugs
Immediate Office
Therapeutics Biologics and Biosimilars Team
10903 New Hampshire Ave.
Silver Spring, MD 20993
301-796-3907 (phone)
Tyree.Newman@fda.hhs.gov

22 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

Reference ID: 3332941

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/s/

TYREE L NEWMAN
06/27/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 202317

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Ceptaris Therapeutics, Inc.
101 Lindenwood Drive
Suite 400
Malvern, PA 19355

ATTENTION: Lisa Wittmer, MS, Ph.D.
Vice President, Global Regulatory Affairs

Dear Dr. Wittmer:

Please refer to your New Drug Application (NDA) dated February 27, 2013, received February 27, 2013, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Mechlorethamine Gel, 0.02%.

We also refer to your April 1, 2013 correspondence, received April 1, 2013, requesting review of your proposed proprietary name, Valchlor. We have completed our review of the proposed proprietary name, Valchlor and have concluded that it is acceptable.

The proposed proprietary name, Valchlor, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your April 1, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sue Kang, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4216. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Tyree Newman at (301) 796-3907.

Sincerely,

{See appended electronic signature page}

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

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/s/

CAROL A HOLQUIST
06/26/2013

Newman, Tyree

From: Newman, Tyree
Sent: Tuesday, June 25, 2013 9:30 AM
To: 'lisa wittmer'
Subject: NDA 202317

Good morning Lisa, please advise us of Ceptaris' postmarketing submission plan (PADER/PSUR), if Valchlor is approved.

Kind regards,

Tyree

Tyree Newman
Sr. Regulatory Health Project Manager
Food and Drug Administration
Office of New Drugs
Immediate Office
Therapeutics Biologics and Biosimilars Team
10903 New Hampshire Ave.
Silver Spring, MD 20993
301-796-3907 (phone)
Tyree.Newman@fda.hhs.gov

Reference ID: 3331738

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/s/

TYREE L NEWMAN
06/26/2013

Newman, Tyree

From: Newman, Tyree
Sent: Monday, June 24, 2013 9:35 AM
To: 'lisa wittmer'
Subject: NDA 202317 - Information request

Good morning Lisa, please provide a response to the following information request by June 26, 2013:

Since the product will be stored at the patients' homes in the refrigerator among the food items, the residue of the product remaining on the tube after use may transfer to foods located next to the product. Thus, potentially this product can be ingested with the food and adverse events may occur. As a result, due to the highly toxic nature of this product, if ingested, we recommend (b) (4)

Kind regards,

Tyree

Tyree Newman
Sr. Regulatory Health Project Manager
Food and Drug Administration
Office of New Drugs
Immediate Office
Therapeutics Biologics and Biosimilars Team
10903 New Hampshire Ave.
Silver Spring, MD 20993
301-796-3907 (phone)
Tyree.Newman@fda.hhs.gov

Reference ID: 3330169

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/s/

TYREE L NEWMAN
06/24/2013

Newman, Tyree

From: Newman, Tyree
Sent: Friday, June 21, 2013 2:28 PM
To: 'lisa wittmer'
Subject: NDA 202317 - Information Request

Good afternoon Lisa, please provide a response to the following information requests by COB, **Friday, June 28, 2013**:

1. Provide the current mobile phase and gradient for the analytical method [redacted] (b) (4) (Identification, assay and impurities). The addendum to the original method validation report (Report YAU-R3754A1) did not specify the changes. Submit the current version of this analytical method to the NDA.

2. Justify with data collected via a flammability test, in accordance with 16 CFR 1500.43, the absence of a flammability warning on the label or add a warning to the label.

3. As per the current policy regarding naming and strength for salt in new products, revise the carton and container labeling to describe the product as "mechlorethamine" [redacted] (b) (4) and the strength as 0.016% [redacted] (b) (4)

Please let me know if you have any questions.

Kind regards,

Tyree

Tyree Newman
Sr. Regulatory Health Project Manager
Food and Drug Administration
Office of New Drugs
Immediate Office
Therapeutics Biologics and Biosimilars Team
10903 New Hampshire Ave.
Silver Spring, MD 20993
301-796-3907 (phone)
Tyree.Newman@fda.hhs.gov

Reference ID: 3329714

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/s/

TYREE L NEWMAN
06/21/2013

Newman, Tyree

From: Newman, Tyree
Sent: Tuesday, May 21, 2013 9:20 AM
To: 'lisa wittmer'
Subject: NDA 202317 - Information request

Good morning Dr. Wittmer, I completed a format review of your labeling regarding NDA 202317 and have the following comments:

- A horizontal line must separate the Highlights (HL) and Table of Contents (TOC) section
- The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading
- 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) - Must include Sponsor phone number**
- A horizontal line must separate the Table of Contents (TOC) from the Full Prescribing Information (FPI) section.
- The preferred presentation for cross-references in the FPI is the section heading followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*]. - (b) (4)
- When clinical trials adverse reactions data is included (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."*
- 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)"

Please make the necessary updates and submit the revised labeling to your NDA by May 27, 2013:

Please inform me if you have any questions.

Kind regards,

Tyree

Tyree Newman
Regulatory Health Project Manager
Food and Drug Administration
Office of New Drugs
Immediate Office
Therapeutics Biologics and Biosimilars Team
10903 New Hampshire Ave.
Silver Spring, MD 20993
301-796-3907 (phone)
Tyree.Newman@fda.hhs.gov

Reference ID: 3313974

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/s/

TYREE L NEWMAN
05/24/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202317

ACKNOWLEDGE –
CLASS 2 RESPONSE

Ceptaris Therapeutics, Inc.
Attention: Lisa Wittmer, M.S., Ph.D.
Vice President, Global Regulatory Affairs
101 Lindenwood Drive, Suite 400
Malvern, PA 19355

Dear Dr. Wittmer:

We acknowledge receipt on February 27, 2013, of your February 27, 2013, resubmission of your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Valchlor™ (mechlorethamine HCl) Gel 0.02%.

We consider this a complete, class 2 response to our May 4, 2012, action letter. Therefore, the user fee goal date is August 27, 2013.

If you have any questions, call me at (301) 796-3907.

Sincerely,

{See appended electronic signature page}

Tyree Newman
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

TYREE L NEWMAN
03/13/2013

Newman, Tyree

From: Newman, Tyree
Sent: Tuesday, May 22, 2012 2:24 PM
To: 'lisa wittmer'
Subject: NDA 202317

Good afternoon Lisa, in response to your email sent on May 10, 2012, regarding your request that the FDA expand on what is meant by “insufficient characterization” in the statement contained in the Complete Response Letter (CRL) for NDA 202-317, the review team has provided the following response:

As discussed in three teleconferences held during the NDA review cycle, the data in total submitted for the clinical and commercial products were insufficient to demonstrate comparability. The insufficiency assessment includes, but is not limited to, absence of impurity data on release and stability for both clinical and commercial products. The issues you identified "*the stability data provided for the retained samples under frozen conditions, the total number of retained samples analyzed, the timing of the testing of the retained samples, the analytical methods utilized and other issues.*" were also included in the assessment.

Kind regards,

Tyree

Tyree Newman
Regulatory Health Project Manager
Food and Drug Administration
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Silver Spring, MD 20993
301-796-3907 (phone)
301-796-9845 (fax)
Tyree.Newman@fda.hhs.gov

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/s/

TYREE L NEWMAN
05/22/2012

Newman, Tyree

From: Newman, Tyree
Sent: Tuesday, April 17, 2012 12:14 PM
To: 'lisa wittmer'
Subject: NDA 202317 - Information Request

Good afternoon Lisa, please confirm by **noon, tomorrow April 18, 2012**, if the following information submitted in your original NDA but absent from your recent CMC amendment, received March 6, 2012, is current and valid.

The name and address of the laboratory performing LC/MS analysis for identity, assay and impurities of the drug product is as follows:

(b) (4)

Kind regards,

Tyree

Tyree Newman
Regulatory Health Project Manager
Food and Drug Administration
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Silver Spring, MD 20993
301-796-3907 (phone)
301-796-9845 (fax)
Tyree.Newman@fda.hhs.gov

Reference ID: 3117704

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/s/

TYREE L NEWMAN
04/17/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202317

DEFICIENCIES PRECLUDE DISCUSSION

Ceptaris Therapeutics, Inc.
Attention: Lisa Wittmer, M.S., Ph.D.
Vice President, Regulatory Affairs
101 Lindenwood Drive, Suite 400
Malvern, PA 19355

Dear Dr. Wittmer:

Please refer to your July 27, 2011, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mechlorethamine Hydrochloride Gel 0.02%.

We also refer to our September 26, 2011, letter in which we notified you of our target date of April 15, 2012, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals And Procedures – Fiscal Years 2008 Through 2012."

As part of our ongoing review of your application, we have identified deficiencies that preclude discussion of labeling and postmarketing requirements/commitments at this time.

This notification does not reflect a final decision on the information under review.

If you have any questions, call Tyree Newman, Regulatory Project Manager, at (301) 796-3907.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, M.D.
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ALBERT B DEISSEROTH
04/13/2012

Newman, Tyree

From: Newman, Tyree
Sent: Wednesday, September 28, 2011 10:02 AM
To: 'Lisa Wittmer'
Cc: Jacqueline Yeager; Pam Morris
Subject: RE: Information request: NDA 202317 site principal investigator information

Good morning Lisa, please clarify who is the inspection contact (name, address, phone, fax, email) at Site 7, NYU. The previous PI (Bruce Strober, MD) is no longer affiliated with NYU.

Please respond by tomorrow, September 29, 2011.

Kind regards,

Tyree

Tyree Newman
Regulatory Project Manager
Food and Drug Administration
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Silver Spring, MD 20993
301-796-3907 (phone)
301-796-9845 (fax)
Tyree.Newman@fda.hhs.gov

From: Lisa Wittmer [mailto:LWittmer@yaupontherapeutics.com]
Sent: Tuesday, September 27, 2011 5:00 PM
To: Newman, Tyree
Cc: Jacqueline Yeager; Pam Morris
Subject: RE: Information request: NDA 202317 site principal investigator information

Tyree,
Please find the information you requested below. Let me know if you need anything else re: inspection contacts at clinical sites.
Lisa

From: Newman, Tyree [mailto:Tyree.Newman@fda.hhs.gov]
Sent: Tuesday, September 27, 2011 9:51 AM
To: Lisa Wittmer
Subject: Information request: NDA 202317 site principal investigator information

Good morning Lisa, please email the following information to my attention: address, phone number, fax number, email address for the principal investigators at the following sites:

1. Site 007: New York University
Principal Investigator: Bruce Strober, MD, PhD

Bruce Strober, MD, PhD

(b) (6)

2. Site 004: Fox Chase Cancer Center
Principal Investigator: Matthew Zook, MD

Dr. Matthew Zook
Fox Chase Cancer Center

(b) (6)

Please this information no later than COB tomorrow, September 27, 2011

Kind regards,

Tyree

Tyree Newman
Regulatory Project Manager
Food and Drug Administration
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Silver Spring, MD 20993
301-796-3907 (phone)
301-796-9845 (fax)
Tyree.Newman@fda.hhs.gov

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/s/

TYREE L NEWMAN
01/13/2012

Newman, Tyree

From: Newman, Tyree
Sent: Tuesday, November 15, 2011 3:09 PM
To: 'Lisa Wittmer'
Subject: NDA 202317 - Information request

Good afternoon Lisa, please address the following information request with the 4-month safety update report (November 23, 2011):

1. The Agency recommends that you submit the following 3 additional datasets (SAS transport format) together with your 4-month safety update report on 23 November 2011.

a. The Agency cannot verify your safety analysis for lymphopenia or neutropenia. **[Dataset 1]** Submit a dataset using the same format as XLB analysis dataset for absolute lymphocyte count and absolute neutrophil count for all patients (one row per laboratory result).

b. For the 4-month safety update, in addition to a written report, the Agency recommends that you submit the datasets for (1) follow-up of non-resolved treatment-emergent AEs as described in Amendment 9 Item 4, and (2) follow-up for SCCA.

For follow-up of above non-resolved skin-related treatment-emergent AEs, include follow-up data regardless of AE relatedness. The Agency cannot rely upon investigator attribution for these skin-related AEs as these are known safety issues with topical NM therapy. **[Dataset 2]** We recommend you use the XAE analysis dataset format for this dataset submission.

How did you collect the information for follow-up for SCCA? The case report forms indicate that these information should have been entered into the DF raw dataset. Analysis of the DF dataset indicates only 2 patients (PT 03-012 and 11-006) with SCCA follow-up greater than 90 days from end of treatment (RFENDT). **[Dataset 3]** We recommend that you use the DF and SUPPDF dataset formats to submit SCCA follow-up information for all patients. Include all dates of follow-up, and indicate whether the SCCA follow-up was made by a medical professional. SCCA follow-up by phone call to the patient would not be acceptable.

2. The clinical review team is unable to run or modify your SAS programs to derive the 95% CI for rate ratios and rate differences.

Please submit a SAS program that will allow the clinical review team to calculate the 95% CI of the rate ratios and rate differences presented in the clinical study report, wherein the input data (c0, S0, c1, S1) would be included with the program statements and would be read through using the CARDS statement.

Comment: c0 and c1 would represent the number of cases (numerator for r=c/S). S0 and S1 would be the total number of subjects per group (denominator for r=c/S).

Please let me know if you have any questions.

Kind regards,

Tyree

Reference ID: 3071995

Tyree Newman
Regulatory Health Project Manager
Food and Drug Administration
Division of Hematology Products
Office of Hematology Oncology Products
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Silver Spring, MD 20993
301-796-3907 (phone)
301-796-9845 (fax)
Tyree.Newman@fda.hhs.gov

Reference ID: 3071995

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/s/

TYREE L NEWMAN
01/13/2012

Newman, Tyree

From: Newman, Tyree
Sent: Wednesday, January 11, 2012 1:24 PM
To: 'Lisa Wittmer'
Subject: NDA 202317 - Information Request

Good afternoon Lisa, please provide a response and the additional datasets to the following by COB, **Tuesday, January 17, 2012** :

1. You have not submitted previously requested data on skin cancer follow-up for all patients in Study 201. The Agency requested for this information on 3 November 2011. Your submission on 24 November 2011 stated that the database containing the update will be locked in early Dec 2011. However, the Agency still has not received the requested data on skin cancer follow-up as of 10 January 2012. The safety evaluation cannot be completed without this information. Provide a status update for this dataset.
2. Appendix G of your submission dated 10 January 2012 (Amendment 16) includes an analysis and comparison of clinical safety of (b) (4) and UIP drug products, however you did not submit a dataset that will allow the Agency to verify this analysis. Submit a modified "interim.xpt" dataset (3727 rows × 30 columns, refer to your 5 October 2011 submission) and include additional columns that include the drug product source (UIP or (b) (4)) and lot number for each row where TAKEU = "Container".

Kind regards,

Tyree

Tyree Newman
Regulatory Health Project Manager
Food and Drug Administration
Division of Hematology Products
Office of Hematology Oncology Products
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Silver Spring, MD 20993
301-796-3907 (phone)
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Tyree.Newman@fda.hhs.gov

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/s/

TYREE L NEWMAN
01/11/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202317 **ACKNOWLEDGE CORPORATE NAME CHANGE**

Ceptaris Therapeutics, Inc.
Attention: Lisa Wittmer, Ph.D.
Vice President, Regulatory Affairs
101 Lindenwood Drive, Suite 400
Malvern, PA 19355

Dear Dr. Wittmer:

We acknowledge receipt on January 6, 2012, of your January 5, 2012, correspondence notifying the Food and Drug Administration that the corporate name has been changed from:

Yaupon Therapeutics, Inc.

to

Ceptaris Therapeutics, Inc.

for the following new drug application:

NDA 202317 for Mechlorethamine Hydrochloride Gel 0.02%.

We have revised our records to reflect this change.

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

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

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

If you have any questions, call me at (301) 796-3907.

Sincerely,

{See appended electronic signature page}

Tyree Newman
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

TYREE L NEWMAN
01/09/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202317 **INFORMATION REQUEST**

Yaupon Therapeutics, Inc.
Attention: Lisa Wittmer, Ph.D.
Vice President, Regulatory Affairs
101 Lindenwood Drive, Suite 400
Malvern, PA 19355

Dear Dr. Wittmer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mechlorethamine Hydrochloride Gel 0.02%.

We also refer to your July 27, 2011 submission, containing the original New Drug Application.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA:

> Microbial limits testing should be conducted at the initial time point (at a minimum) on stability batches according to USP <61>/<62> methodology or equivalent. The microbial limits specification should be consistent with USP <1111> recommendations for cutaneous use. Once a satisfactory product history has been established, a post-approval supplement may be submitted to the FDA requesting a waiver of microbial limits testing of stability batches.

If you have any questions, call Scott N. Goldie, Ph.D., Senior Regulatory Project Manager for Quality, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Sarah C. Pope Miksinski, Ph.D.
Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

SARAH P MIKSINSKI
01/05/2012

MEMORANDUM OF TELECONFERENCE

Date: December 16, 2011

Subject: NDA 202317 – Response to December 8, 2011- Teleconference

FDA Attendees (Agency):

Ann Farrell, M.D., Division Director (Acting; DHP)
Edvardas Kaminskas, M.D., Deputy Director (Acting; DHP)
Albert Deisseroth, M.D., Medical Team Leader (Acting; DHP)
Anne Marie Russell, Ph.D., Product Quality Reviewer (ONDQA)
R. Angelo De Claro, M.D., Medical Officer (DHP)
Sarah Pope Miksinski, Ph.D., Branch Chief (ONDQA)
Gaetan Ladouceur, Ph.D., Product Quality Reviewer (ONDQA)
Yash Chopra, Ph.D., Pharmacology/Toxicology Reviewer (DHOT)
Janice Brown; Ph.D., CML-Lead (ONDQA)
John Leighton, Ph.D., Division Director (Acting; DHOT)
Richard Lostritto, Ph.D., Division Director (ONDQA)
Haleh Saber, Ph.D., Pharmacology/Toxicology Supervisor (DHOT)
Rachelle Lubin, Pharm.D., Clinical Pharmacology Reviewer (DCPV)
Tyree Newman, Regulatory Project Manager (DHP)

Yaupon Therapeutics (Sponsor):

Marty Stogniew, Ph.D. – Vice President, Pharmaceutical Sciences
Tim Henkel, MD, Ph.D. – Executive Vice President and Head of Research and Development
Jim Dowell, Ph.D. – Vice President, Biopharmaceutics
Jeff Wilkins, M.D. – Chief Medical Officer
Lisa Wittmer, Ph.D. – Vice President, Regulatory Affairs

Background:

On December 16, 2011, a teleconference was conducted between the FDA and Yaupon Therapeutics (Sponsor) to have further discussion regarding the responses from Yaupon to the Information Request for NDA 202317 dated December 1, 2011 and the teleconference between Yaupon and the Agency on December 8, 2011. Yaupon provided the attached slides submitted to the FDA on December 15, 2011.

Discussion Items:

The teleconference began with Yaupon summarizing the following points (noted on the slides):

A. Justification for comparability of the (b) (4) and UIP drug products:

(b) (4)

(b) (4)

B. Potential additional approaches to demonstrate comparability of the (b) (4) and UIP drug products:
   1. Based upon the justification above, utilize UIP assay and impurity data and (b) (4) assay data to predict the impurity levels in (b) (4) lots within the same time window
      - Compare predicted impurities to measured impurities

      (b) (4)
   2. Measure impurities in (b) (4) lots used in the clinical trials (b) (4)

The FDA responded with the following questions:

- Please clarify comment #3, bullet 3
  - Yaupon will provide the appropriate literature clarifying the statement in a January 2012 submission to the NDA.
- What do you know about the stability of the product (b) (4)?
  - Yaupon will submit the data to the FDA in the January 2012 submission.

The FDA explained that most frost-free refrigerators at home are not the same as laboratory freezers.

- The Sponsor confirmed the product was stored (b) (4) in a lab freezer, and tested with cycling freeze and thaw.
  - Yaupon will submit data to the FDA in the January 2012 submission to justify updated storage temperatures.

The FDA inquired Yaupon to respond to the following questions and comments:

(b) (4)

- Was there a signal from the assay test regarding the stability of the product?
  - Yaupon stated they did not see impurities based on their derivative based detection method.
- The FDA requested Yaupon to provide Assay chromatograms; preferably from samples which show low Assay results, to the NDA for review.
  - Yaupon will submit the data to the FDA
- The FDA requested Yaupon to forward the raw data from the Tables

- Yaupon will submit the data to the FDA

Yaupon offered to provide a per patient breakdown log by safety and efficacy.

Dr. Farrell restated to Yaupon that the primary issues they must address are as follows:

- Clinical and Commercial product bridging
- Impurity profile of clinical product
- The Sponsor must keep in mind that in order to have a product, we must be able to write a label based on the data.
- Yaupon should provide all data they believe would assist the Agency to conduct a comprehensive review.

Action Items:

- The Sponsor will submit all requested information in a January submission to the IND.
- The Sponsor may request a possible face-to-face meeting.

APPEARS THIS WAY ON ORIGINAL

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/s/

TYREE L NEWMAN
01/03/2012

MEMORANDUM OF TELECONFERENCE

Date: December 8, 2011

Subject: NDA 202317 – December 1, 2011 - Information Request (impurity data)

FDA Attendees (Agency):

Ann Farrell, M.D., Division Director (Acting; DHP)
Edvardas Kaminskas, M.D., Deputy Director (Acting; DHP)
Anne Marie Russell, Ph.D., Product Quality Reviewer (ONDQA)
R. Angelo De Claro, M.D., Medical Officer (DHP)
Gaetan Ladouceur, Ph.D. Product Quality Reviewer (ONDQA)
Yash Chopra, Ph.D., Pharmacology/Toxicology Reviewer (DHOT)
Janice Brown; Ph.D., CMC-Lead (ONDQA)
John Leighton, Ph.D., Division Director (Acting; DHOT)
Richard Lostritto, Ph.D., Division Director (ONDQA)
Haleh Saber, Ph.D., Pharmacology/Toxicology Supervisor (DHOT)
Robert White Jr., M.D., Medical Officer (DOP2)
Tyree Newman, Regulatory Project Manager (DHP)

Yaupon Therapeutics (Sponsor):

Marty Stogniew, Ph.D. – Vice President, Pharmaceutical Sciences
Tim Henkel, MD, Ph.D. – Executive Vice President and Head of Research and Development
Jim Dowell, Ph.D. – Vice President, Biopharmaceutics
Jeff Wilkins, M.D. – Chief Medical Officer
Pam Morris – Director, Clinical Research
Lisa Wittmer, Ph.D. – Vice President, Regulatory Affairs
Jaci Yeager – Associate, Regulatory Affairs
(b) (4) Regulatory CMC Consultant

Background:

On December 8, 2011, a teleconference was conducted between members from the Agency and Yaupon Therapeutics (Sponsor) to discuss the Information Request for NDA 202317 submitted to Yaupon Therapeutics on December 1, 2011. The request focused on questions and clarifications from a Clinical, CMC and Non Clinical perspective. The response to the Information Request was provided to the Agency on December 8, 2011.

Discussion Items:

The FDA informed Yaupon that we had just received their response to our joint clinical, chemistry and pharmtox information requests. The FDA acknowledged the Sponsor's confirmation that no impurity data was collected on the (b) (4) clinical lots used in the pivotal study. The FDA also stated that this was in contrast to Agency advice in several meetings throughout drug development. The implications of this lack of impurity data are significant and affect multiple disciplines of the NDA review. As a consequence of this missing data, there is no

adequate bridge between the clinical product administered to patients in the pivotal trial and the commercial product the Sponsor proposes to market.

Yaupon requested clarification of the timing of FDA advice to collect impurity data on pivotal clinical supplies during drug development. FDA stated that CMC advice to characterize drug product on release and stability had been advised at the time of IND submission in 2004, at the CMC meeting in 2006 and at the pre-NDA CMC meeting in 2010.

(b) (4)

Further, FDA advised that this quality issue affected the acceptability for regulatory action the safety and efficacy results of the Phase 2 clinical trial, Study-201. Because the quality of the clinical supplies was not sufficiently characterized to demonstrate comparability with the proposed commercial product, the results of Study-201 could not serve as the basis for a label written for the commercial product.

Yaupon requested advice on addressing this quality issue. FDA stated that a new randomized clinical trial that established the efficacy and safety of the commercial product was an option. FDA clarified that a Phase 1 trial or nonclinical study would not be adequate.

Yaupon issued a new proposal (b) (4)

Yaupon explained that several members of their current team were not involved with the earlier meetings/discussions and their interpretation of the minutes led them to believe it was OK to submit the NDA without the stability data. FDA responded that it is up to the Sponsor to provide all of the information that they believe the Agency will need to review the application which should have included the required stability data.

The Sponsor stated that their current commercial lot is better than the clinical lot. FDA commented that they appreciate the Sponsor's effort to have a better product however; from a CMC perspective, FDA is unable to bridge the data from the clinical product to the commercial product.

Yaupon inquired if there was anything they could do to address the lack of stability data? FDA responded that there is no way they can go back in time to obtain the data that was not captured and compare it to the stability of the commercial product. The FDA suggested that the Sponsor

may have to do another clinical trial (new clinical data set). The FDA stated from a clinical perspective, based on the unavailability of the stability data, we can not justify the safety and efficacy of the current commercial product.

Yaupon inquired how Yaupon would use the stability data to make a determination about the commercial product if it were present. The FDA (ONDQA) responded that it would conduct a review of the data and make a determination if the stability was consistent and provide their recommendation to members of the review team on the stability of the product. Yaupon inquired if their assay method could be used to justify the impurity profile between both the clinical and commercial batches which they felt was similar at various time points. Yaupon stated that the assay method is not designed to quantify or validate the impurity profile and the method must also be validated.

FDA emphasized that in order for them to approve the product, the labeling of the product must be drafted based on the clinical studies that were conducted.

Yaupon requested to submit a proposal in response to this teleconference. FDA agreed and asked for a planned submission date. Yaupon said they would take a few days to formulate a plan and would provide an estimated submission date for their response in a few days. The FDA agreed to review their proposal once it has been made available.

Action Items:

The Sponsor will follow-up with Tyree Newman to inform the FDA when they can expect to receive their proposal.

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/s/

TYREE L NEWMAN
01/03/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202317

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Yaupon Therapeutics, Inc.
101 Lindenwood Drive
Suite 400
Malvern, Pennsylvania 19355

ATTENTION: Lisa Wittmer, MS, Ph.D.
Vice President, Regulatory Affairs

Dear Dr. Wittmer:

Please refer to your New Drug Application (NDA) dated July 27, 2011, received July 27, 2011, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Mechlorethamine Hydrochloride Gel, 0.02%.

We also refer to:

- your September 28, 2011, correspondence, received October 3, 2011, requesting review of your proposed proprietary name, Valchlor.
- and your December 7, 2011, amendment, received December 7, 2011, to your request for name review.

We have completed our review of Valchlor and have concluded that it is acceptable.

Valchlor will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your September 28, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sue Kang, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4216. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Tyree Newman at (301) 796-3907.

Sincerely,

{See appended electronic signature page}

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

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/s/

CAROL A HOLQUIST
12/20/2011

Newman, Tyree

From: Newman, Tyree
Sent: Thursday, December 01, 2011 3:19 PM
To: 'Lisa Wittmer'
Subject: RE: NDA 202317 - Information Request

Hi Lisa, we are requesting a response by Tuesday, 12/6. Yes, these will be the topics for the T-con. Main issues for discussion will be topics 1-3.

Kind regards,

Tyree

Tyree Newman
Regulatory Health Project Manager
Food and Drug Administration
Division of Hematology Products
Office of Hematology Oncology Products
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Silver Spring, MD 20993
301-796-3907 (phone)
301-796-9845 (fax)
Tyree.Newman@fda.hhs.gov

From: Lisa Wittmer [mailto:LWittmer@yaupontherapeutics.com]
Sent: Thursday, December 01, 2011 1:59 PM
To: Newman, Tyree
Subject: RE: NDA 202317 - Information Request

Hi Tyree,
I can confirm receipt of this request. I have two questions relating to the request: 1) are these the topics for the upcoming teleconference and 2) is FDA requesting a response by December 13th?
Thank you,
Lisa

From: Newman, Tyree [mailto:Tyree.Newman@fda.hhs.gov]
Sent: Thursday, December 01, 2011 11:20 AM
To: Lisa Wittmer
Subject: NDA 202317 - Information Request

Good morning Lisa, please provide a response to the following by COB, **Tuesday, December 3, 2011**:

1. **Confirm that impurity data was not collected at release and on stability for the (b) (4) clinical lots, which supplied (b) (4) the clinical doses. Alternately, provide release**

and stability impurity batch data for all (b) (4) clinical lots. Include information on the analytical method used to collect the data.

2. **It is not clear how the clinical data submitted is able to justify the specifications proposed for impurities in the drug product. The impurity data analysis submitted in Table (3.2.P.5.6.8)2 titled "Summary of Ranges of Impurities in Yaupon Formulation and Associated ICH Identification and Qualification Thresholds" was performed on data collected on lots which were not used in clinical or non-clinical studies. Further, the referenced 3 UIP stability lots in the table were manufactured at a different site, by a different manufacturer, by a different process, at a different scale and packaged into a different size tube than the clinical lots. (b) (4) Provide clarification of your justification of the drug product specifications.**
3. **Describe the storage conditions from time of release until testing for each lot listed in Table (3.2.P.2.3.3)1 titled " (b) (4) and UIP lots tested using the proposed NDA Methods". Provide convincing scientific justification for relating the impurity levels of these lots to support your proposed comparability (b) (4) Justification should include discussion of changes to storage temperature, stability, differences in manufacturing site, process, scale and differences in tube size.**
4. **Provide a status update of clinical trial 2007NMMF-202-US (number of patients enrolled, number of patients still on treatment, number of patients on follow-up).**
5. **Your estimated maximum daily dose (b) (4) is not consistent with datasets submitted on 17 October 2011. (b) (4) Clarify the maximum daily dose that you propose to use for calculation of impurity levels.**

Kind regards,

Tyree

Tyree Newman
Regulatory Health Project Manager
Food and Drug Administration
Division of Hematology Products
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/s/

TYREE L NEWMAN
12/02/2011

MEMORANDUM

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

DATE: November 14, 2011

TO: NDA 202317 file

FROM: Tyree Newman

SUBJECT: Applicant Orientation Meeting

APPLICATION/DRUG: NDA 202317/VALCHLOR™ (mechlorethamine HCl) Gel 0.02%

On October 6, 2011, Yaupon Therapeutics Inc. (sponsor) presented the attached slides during the Applicant Orientation meeting for NDA 202317.

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/s/

TYREE L NEWMAN
11/14/2011

Newman, Tyree

From: Newman, Tyree
Sent: Thursday, November 03, 2011 12:40 PM
To: 'Lisa Wittmer'
Subject: NDA 202317 Information Request

Good afternoon Lisa, please address the following information request by COB on **Monday, November 15, 2011**:

1. What is the data cut-off date for the efficacy analysis?

2. What is the data cut-off date for the safety analysis?

3. Only 2 patients had follow-up >90 days following completion of treatment for surveillance of secondary skin cancers. Page 105 of the CSR states "Complete follow-up data on the occurrence of skin cancers through the entirety of the 12 month follow up period for remaining patients will be reported as a future addendum to this study report." We note that all patients completed treatment by July 2010, and hence the additional 12 month follow-up data should have been available by July 2011. We recommend that you submit this addendum as soon as possible.

4. Several patients (almost 25% of all patients in the clinical trial) with a treatment-emergent skin-related AE (where AEDRLES field contains "Generalized dermal irritation", "Local dermal irritation", "Local dermal irritation with secondary infection", "Severe local dermal irritation", "Skin infection – bacterial", or AEDECOD contains "Folliculitis" or "Staphylococcal infection") have no end date for the AE, and are therefore considered to have unresolved AEs. Provide additional follow-up data for these unresolved AEs for both treatment arms. If no additional follow-up information is available, provide justification that persistence of these AEs in 20-25% of all patients confers a favorable benefit-risk profile for your drug.

5. You are required to submit a safety update report 4 months after the initial submission as per 21CFR314.50(d)(5)(vi)(b). When do you intend to submit the safety update report? What do you intend to include in the safety update report? We recommend that you include items 3 and 4 with the safety update report.

6. Describe the procedure on the filling out of the pathology case report forms for <u>each local and central pathology site</u>. Who transcribed the pathology reports onto the pathology case report forms?

7. Pautrier's microabscess (PM) were noted in more than 60% of patients on both local and central pathology review. The reported prevalence of PM in early mycosis fungoides is about 20-30%.

Table 1. Presence of Pautrier's microabscesses (PM) in patients with early MF

Reference	Number of Biopsies	Number with PM	% with PM
Santucci, 2000	24	1	4%
Shapiro, 1994	186	32	17%
Smoller, 1995	64	24	37%
Naraghi, 2003	24	9	37.5%
Nickoloff, 1988	228	66	29%
Massone, 2005	745	140	19%

Table 2. Presence of Pautrier's microabscesses (PM) in 2005NMMF-201-US

	Number of Patients	Number with PM	% with PM

Reference ID: 3039059

Local pathology review	260	165	63%
Central pathology review	260	161	62%

Explain the discrepancy in the presence of PM in Study 201 compared to literature data.

8. Your clinical study report, the statistical analysis plan, and/or the protocol provide inconsistent information on the following issues. Please clarify:

8.1. Is 2005NMMF-201-US a single- or double-blinded clinical trial?

8.2. Is the primary endpoint CAILS overall response at 12 months or within up to 12 months?

9. Your last protocol amendment was on 12/8/08. However, your statistical analysis plan is dated 8/15/08. Was the 8/15/08 SAP the final version? If not, submit the final SAP version in clean and track change format.

10. CTCAE Grade 1 toxicity for neutropenia and lymphopenia is defined based on the LLN for neutrophil and lymphocyte counts. How did you calculate the LLN for neutrophil and lymphocyte counts?

11. The study report indicates that the wife of one of the participating subjects (003-0032-AP) became pregnant between 1 and 2 months after the subject initiated treatment, and that the pediatrician provided a letter documenting that the baby was carried to term (38 weeks) and was completely healthy. We recommend that you submit the pediatrician's letter for review.

Kind regards,

Tyree

Tyree Newman
Regulatory Health Project Manager
Food and Drug Administration
Division of Hematology Products
Office of Hematology Oncology Products
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
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Reference ID: 3039059

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/s/

TYREE L NEWMAN
11/03/2011

Newman, Tyree

From: Newman, Tyree
Sent: Tuesday, September 27, 2011 9:51 AM
To: 'Lisa Wittmer'
Subject: Information request: NDA 202317 site principal investigator information

Good morning Lisa, please email the following information to my attention: address, phone number, fax number, email address for the principal investigators at the following sites:

1. Site 007: New York University
Principal Investigator: Bruce Strober, MD, PhD

2. Site 004: Fox Chase Cancer Center
Principal Investigator: Matthew Zook, MD

Please this information no later than COB tomorrow, September 27, 2011

Kind regards,

Tyree

Tyree Newman
Regulatory Project Manager
Food and Drug Administration
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
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/s/

TYREE L NEWMAN
09/29/2011

Newman, Tyree

From: Newman, Tyree
Sent: Thursday, September 29, 2011 10:54 AM
To: 'Lisa Wittmer'
Subject: NDA 202317: Information Request and AOM Presentation Request

Good morning Lisa, please provide the following by **Monday, October 3, 12pm EST**:

1. Submit a dataset which contains the following information for all 260 patients.

1.1. USUBJID
1.2. Informed Consent Date
1.3. Original Randomization Date
1.4. Original Randomization Treatment Arm
1.5. Rerandomization Date
1.6. Rerandomization Treatment Arm

2. Submit all CRF pages with local and central pathology data for all patients. We recommend that you use the same format when you submitted all the pathology reports (one PDF file per site).

3. Also, for next week's Meeting we would like you to also address the following:

- Discuss the intra-patient correlation between the best CAILS and SWATS response. Specifically, discuss patients classified as responders on CAILS score but as non-responders on SWAT score, and vice-versa.
- Provide justification for the non-inferiority margin.
- Present data on the maximum, average, and range of the amount of drug product used.

Please inform me if you have any questions.

Thank you,

Tyree

Tyree Newman
Regulatory Project Manager
Food and Drug Administration
Division of Hematology Products
Office of Hematology Oncology Products
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/s/

TYREE L NEWMAN
09/29/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202317

FILING COMMUNICATION

Yaupon Therapeutics, Inc.
Attention: Lisa Wittmer, M.S., Ph.D.
Vice President, Regulatory Affairs
101 Lindenwood Drive, Suite 400
Malvern, PA 19355

Dear Dr. Wittmer:

Please refer to your New Drug Application (NDA) dated July 27, 2011, received on July 27, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Mechlorethamine Hydrochloride Gel 0.02%.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is May 27, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by April 15, 2012.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

1. Submit the following drug substance information:
   i. A summary on the actual and potential impurities in the drug substance (b) (4) [redacted] Include a justification for setting the acceptance criteria for individual and total impurities and how the proposed limits are qualified. Submit

the results of impurity identification and degradation products greater than the identification threshold in any batch manufactured by the proposed commercial process.

ii. Submit the results of drug substance stress testing. As described in ICH Q1A(R2), data should include the effects of temperature, pH, humidity, oxidation and photostability of the drug substance.

iii. If the DMF holder has performed the studies requested in 1a and 1b, you may submit a letter of authorization from the drug substance manufacturer allowing the agency to reference the confidential information in their DMF.

2. As described in ICH Q6A, the drug product specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria. Submit a revised drug product specification to include a reference to the analytical method.

3. Provide a comparison of the relative amounts of the two different products ((b) (4) tube and UIP 60 g tube) used in the pivotal clinical trial. Include the following information for each lot listed in Table (3.2.P.5.4)1 - Batch Analysis of Drug Product Clinical Lots:
   i. Number of units released (e.g. (b) (4) 60g tubes).
   ii. Number of units dispensed in the pivotal clinical study.
   iii. Number of units consumed in the pivotal clinical study.

4. Most of the PDF documents do not contain recognizable text which can be copied. This issue results in unnecessary delays and can affect the overall efficiency of the review.

   When submitting PDF documents it's important to comply with Portable Document Format Specifications (PDF - 57KB)[22] (6/4/2008). Also, please review section J on page 8 in the Final Guidance for Industry: Providing Regulatory Submissions in Electronic Format—Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications (PDF - 132KB)[13] (June 2008).

   Please re-submit the documents in module 3 and the QOS in module 2 which were previously submitted to NDA 202317 that didn't contain recognizable text that can be copied and ensure the new PDF documents contain text that can be copied. The submission should be an amendment to NDA 202317 and you should include a statement in the cover letter attesting that the content didn't change from what was previously submitted and only the format changed.

5. Provide the results of (b) (4) testing on three lots of drug product using (b) (4) methodology or equivalent.

6. Provide the microbial limits specification and test method for the finished drug product in section 3.2.P.5.1 of the application. The acceptance criteria for cutaneous use drug products provided in USP <1111> are recommended.

7. The sponsor should provide justification for non-inferiority margin used in the study 2005NMMF-201-US.

8. For the 9 patients who were re-randomized due to change in disease status, clarify how the patient was included in ITT, per initial randomized treatment or final randomized treatment?

9. For the safety analyses, clarify whether patients were analyzed per treatment actually received.

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

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

We acknowledge receipt of your request for a full deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full deferral request is denied.

If you have any questions, call Tyree Newman, Regulatory Project Manager, at (301) 796-3907.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, M.D.
Director (Acting)
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

ANN T FARRELL
09/26/2011

Newman, Tyree

From: Newman, Tyree
Sent: Wednesday, September 21, 2011 3:04 PM
To: 'Lisa Wittmer'
Subject: NDA 202317 - Information request

Good day Lisa, please provide a response to the following queries by Monday, October 3, 2011 (9AM EST):

1. You did not submit data on the dose (amount of drug product) received for patients in Study 201. Your exposure datasets captured only frequency of doses. The dose received is required for the product quality review, clinical review, and labeling. Submit a dataset which contains the average daily amount of drug product used for all patients per assessment period (between visits) in Study 201. The amount of drug product used per assessment period may be calculated based on the refill amount and frequency.

We remind you that the above information should have been collected as per Section 9.2 Dispensing and Accountability of the protocol. Specifically, the protocol states "The number of the containers being dispensed, the patient identification number and initials, and the date dispensed, will be recorded on the Drug Inventory Form."

2. Submit instructional materials provided to patients and/or investigators regarding the method of topical application of the NM ointment.

Please inform me if you have any additional questions.

Kind regards,

Tyree

Tyree Newman
Regulatory Project Manager
Food and Drug Administration
Division of Hematology Products
Office of Oncology Drug Products
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Reference ID: 3018486

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/s/

TYREE L NEWMAN
09/21/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202317 **INFORMATION REQUEST**

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Yaupon Therapeutics, Inc.
Attention: Lisa Wittmer
101 Lindenwood Drive, Suite 400
Malvern, PA 19355

Dear Dr. Wittmer:

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

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).[1] The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or "prep" run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or "prep" runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

[1] These violations include studies conducted by Bioassay Laboratories and BA Research International specific to the Houston, Texas facility.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Alice Kacuba, Chief, Project Management Staff, at (301) 796-1381.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

ALICE KACUBA
09/16/2011
Signing for Dr. Justice.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202317

NDA ACKNOWLEDGMENT

Yaupon Therapeutics, Inc.
Attention: Lisa Wittmer, M.S., Ph.D.
Vice President, Regulatory Affairs
101 Lindenwood Drive, Suite 400
Malvern, PA 19355

Dear Dr. Wittmer:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Mechlorethamine Hydrochloride Gel 0.02%

Date of Application: July 27, 2011

Date of Receipt: July 27, 2011

Our Reference Number: NDA 202317

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 25, 2011, in accordance with 21 CFR 314.101(a).

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

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

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

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

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

If you have any questions, call Tyree Newman, Regulatory Project Manager, at (301) 796- 3907.

Sincerely,

{See appended electronic signature page}

Tyree Newman
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

TYREE L NEWMAN
09/08/2011

Newman, Tyree

From: Newman, Tyree
Sent: Wednesday, September 07, 2011 2:53 PM
To: 'LWittmer@yaupontherapeutics.com'
Cc: Fagbami, Modupe
Subject: NDA 202317: Information Request

Good day Dr. Wittmer, my name is Tyree Newman and I will be replacing Modupe Fagbami as your primary contact regarding NDA 202317. We are currently reviewing your NDA and would like you to respond to the following queries by **COB Thursday, September 8, 2011**:

- Considering that the pathology reports for both the local and confirmatory reviews have been retained at the study sites as source documentation, please provide the pathology reports (i.e., local, independent local, and confirmatory pathology reports) for all the patients in Study 201.

- For the Algorithm Diagnosis, in the independent local review and the confirmatory review, what is the source of the molecular biological and immunopathological data, i.e., are the data for each review derived from different sources or the same source?

- In Appendix 16.1.4 List of Investigators and Other Important Study Participants, [redacted] (b) (6) is listed as a confirmatory pathologist. The Stanford group is not listed as the back-up for review of the Fox Chase pathology specimens. Please clarify.

- On page 30 of the Clinical Study Report, it states that if a patient's disease was reassessed at baseline and the stage was upgraded, the patient was re-randomized (stage assessment in pre-screening→randomization→stage reassessment @ baseline > @ pre-screening→re-randomization). And if the disease progressed beyond Stage IIA, then the patient was withdrawn from the study (stage assessment in pre-screening→randomization→stage reassessment @ baseline > IIA→withdrawn). Pages 31-32 of the protocol and APPENDIX 3: FLOW CHART OF STUDY ACTIVITIES (page 71) (revised 12/08/08) appear not to support these procedures for re-randomization. The protocol states that randomization occurs late in the baseline evaluation and there does not appear to be a provision for re-randomization or withdrawal of the patient in the event of advancing stage in the pre-study to baseline visit period. Please indicate the whereabouts of re-randomization or double-randomization in the protocol.

- Please indicate the patients: 1) whose stage progressed in the interval from pre-study to baseline visit, 2) who were re-randomized (indicate the initial randomization arm and the re-randomization arm), and 3) who were withdrawn because their stage of disease progressed beyond IIA. Indicate when drug was dispensed (i.e., at 1st randomization, at 2nd randomization, or both). Include the dates of both randomizations and the stage changes. Also, provide the case report forms for these patients.

- Please provide the case report forms for the Oklahoma University site (center 8).

- Do you have financial disclosure on the investigators who were "Listed on previous 1572s"?

- It is noted that the previous study coordinator/pharmacist at the NYU site was not listed on the form 3454. Please provide the financial disclosure forms for this person.

- Your financial disclosure attachments to form 3454 did not list the study coordinators/pharmacists, who were involved with the study, at all the study sites, (i.e., Brigham & Women's, MD Anderson, Stanford, Fox Chase, Duke, Univ. of Penn., Oklahoma U, Southwestern Medical). Please clarify, correct and indicate

Reference ID: 3011646

their financial disclosure status.

- In your collection of data from investigators and study site personnel, you queried them about receipt of financial interests but limited the inquiry to within the past year. In view of the misunderstanding that one of the investigators had about financial disclosure, re-query the investigators concerning financial disclosure within the course of the entire study and for one year after completion of the study.

- In Appendix 16.1.7 Randomization Codes, the tables lack the subject numbers and dates. Please fill-in the blanks.

- Submit a CONSORT flow diagram (refer to http://www.consort-statement.org/consort-statement/flow-diagram0/) that details the disposition of each patient in Study 201, including screening failures.

Please inform me if you have any questions.

Kind regards,

Tyree

Mr. Tyree Newman
Regulatory Project Manager
Food and Drug Administration
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Silver Spring, MD 20993
301-796-3907 (phone)
301-796-9845 (fax)
Tyree.Newman@fda.hhs.gov

Reference ID: 3011646

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/s/

TYREE L NEWMAN
09/07/2011

From: Fagbami, Modupe
Sent: Tuesday, August 30, 2011 8:29 PM
To: 'Lisa Wittmer'
Subject: NDA 202317 Mechlorethamine Hydrochloride: Clinical Information Request
Importance: High

Dear Ms Wittmer,

Please find the following clinical information request for your response on or before 4:00 pm on Wednesday, August 31, 2011.

- Age > 18 years was an inclusion criterion in the first protocol submitted for special protocol assessment (sequence #001; date: 12/1/2004). Age > 18 was deleted from the protocol in the second round of special protocol assessment (sequence #005; date: 9/13/2005). Please provide a rationale for removal of this criterion. And what age range was actually eligible for your pivotal study?

- In your NDA, you provided audit certificates for four sites. Were other sites audited? In general, were reports generated for the audits?

- With regard to the randomization problem, please provide the report generated for the NYU site.

- Thank you for providing the financial disclosure forms (b) (6) (b) (4) Please provide the financial disclosure forms

- It is not clear how the dates for both the independent local pathology review and the confirmatory independent pathology review were performed and recorded on the same date, particularly, if by histological criteria, the diagnosis was not made and the algorithm for diagnosis was employed. Also, the algorithm has clinical criteria. How did the independent dermatopathologists satisfy these criteria, particularly, the confirmatory independent dermatopathologist, who was not at the same site as the patient?

- Patient #003-0003 was a discordant case. With subscores by histological criteria or a non-diagnostic and non-consistent for mycosis fungoides determination by the local dermatopathologist, it is unclear why the local dermatopathologist did not follow the algorithm for diagnosis. Please clarify. Also, please provide copies of both the local and confirmatory reviews for this patient.

Please let me know if you have any questions.

Thank you.

Modupe O. Fagbami
RPM
Division of Drug Oncology Products
Office of Oncology Drug Products
CDER, FDA
10903 New Hampshire Avenue
WO-22, Room 2108
Silver Spring, Maryland 20993
Phone: 301-796-1348
Fax: 301-796-9845

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/s/

MODUPE O FAGBAMI
08/31/2011

From: Fagbami, Modupe
Sent: Monday, August 29, 2011 1:12 PM
To: 'Lisa Wittmer'
Subject: NDA 202317 Mechlorethamine Hydrochloride Gel Statistics Information Request
Importance: High

Dear Ms. Wittmer,

We noticed that you submitted data but not statistical programs for analysis. Kindly submit supporting programs for statistical analysis?

Please let me know if you have any questions.

Thank you

Modupe O. Fagbami
RPM
Division of Drug Oncology Products
Office of Oncology Drug Products
CDER, FDA
10903 New Hampshire Avenue
WO-22, Room 2108
Silver Spring, Maryland 20993
Phone: 301-796-1348
Fax: 301-796-9845

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/s/

MODUPE O FAGBAMI
08/29/2011

From: Fagbami, Modupe
Sent: Friday, August 26, 2011 9:08 AM
To: 'Lisa Wittmer'
Cc: Jacqueline Yeager
Subject: NDA 202-317, topical nitrogen mustard: Information Request

Hi Lisa,

Please find the following information request for your quick response on or before 4: 00 pm, Monday, August 29, 2011.

- Where on the case report form is the information recorded, regarding the baseline skin biopsy reviews by the two independent pathologists? Where are the pathology reports? Who were the two independent pathologists? Was financial disclosure information collected on them? How many patients failed the independent pathology review?

- In the figure below, it appears that additional biopsies (@ baseline, monthly, and then q 2 months) were performed. Please indicate the whereabouts of the biopsy results.

Table 2: Flow of Study Activities

ASSESSMENT TO BE COMPLETED	Pre-Study Up to 90 days Before Day 1	Pre-Study Up to 30 days Before Day 1	Prior to Day 1	Day 1 "Baseline" 1st Rx Day	Week 4	Every Month to Month 6 Every 2 Months To Month 12	Extended Tox Evaluation for an additional 12 months
MF Confirmed by Biopsy	X (NOTE 2)			X		X	

- Please provide the patient number of the patient illustrated in the poster presented at the First World Congress of Cutaneous Lymphomas (9/2011).

- APPENDIX 16.1.1 PROTOCOL AND PROTOCOL AMENDMENTS (of Protocol 2005NMMF-201-US – Clinical Study Report) has links to 6 different versions of the protocol. Is there a red-lined version of the protocol in order to clearly see the changes that were made or a summary table of the changes that were made?

Please let me know if you have any questions.

Thank you.

Modupe O. Fagbami

RPM
Division of Drug Oncology Products
Office of Oncology Drug Products
CDER, FDA
10903 New Hampshire Avenue
WO-22, Room 2108
Silver Spring, Maryland 20993
Phone: 301-796-1348

Fax: 301-796-9845

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/s/

MODUPE O FAGBAMI
08/26/2011

MEETING MINUTES

MEETING DATE: December 21, 2010 **TIME:** 10: 00 am

LOCATION: WO Building 22, Room 1309

IND: 067839

Meeting Request Submission Date: September 10, 2010

Briefing Document Submission Date: November 19, 2010

FDA Response Date: December 13, 2010

DRUG: Nitrogen Mustard

SPONSOR: Yaupon Therapeutics, Inc.

TYPE of MEETING: Type B, Pre-NDA Meeting (Face to Face)

INDICATION: Treatment of Mycosis fungoides

FDA PARTICIPANTS:

Edvardas Kaminskas, M.D. Acting Deputy Director, DHP
John R. Johnson M.D., Medical Officer, Team Leader, DDOP-Meeting Chair
Robert White, M.D., Clinical Reviewer, DDOP
Sara Pope Miksinski, Ph.D., Branch Chief, ONDQA
Haripada Sarker, Ph.D., Pharmaceutical Assessment Lead, ONDQA
Shenghui Tang, Ph.D., Team Leader, Biostatistics, Division of Biostatistics DBV
Modupe Fagbami, Regulatory Health Project Manager, DDOP

INDUSTRY PARTICIPANTS:

Robert Alonso, President & CEO
Martin Stogniew, PhD, Chief Technology Officer
Phil Schein, MD, Acting Chief Medical Officer
Pam Morris, Director, Clinical Trials
Henry Mok, Ph.D., Director, Manufacturing/CMC
Jacqueline Yeager, Regulatory Affairs Associate
(b) (4) Statistical/Regulatory Consultant
(b) (4) Regulatory Affairs Consultant
(b) (4)
(b) (4) Regulatory Affairs Consultant

BACKGROUND:

The IND was submitted on September 30, 2004. There had been 5 Special Protocol No-Agreements. Sponsor is requesting this meeting to request feedback from the Agency on the

specific items as described in the meeting package regarding the format and content to support the filing of the 505(b)(2) NDA.

Yaupon is planning to submit a 505(b)(2) New Drug Application (NDA) for its proprietary topical formulation containing Mechlorethamine HCl (0.02% w/w), the same active substance contained in Mustargen® (NDA#6695) which will be referenced as the Listed Drug.

Yaupon has obtained a pre-assigned NDA#202-317 for the submission.

All sections of the NDA will be prepared in accordance with the ICH Common Technical Document (CTD) format. Yaupon has also obtained a waiver (from CDER eSub) for submission of non-eCTD electronic "hybrid" submission (see **Attachment 1**).

A proposed comprehensive NDA Table of Contents is provided here in **Attachment 2**. Additional background information is prepared below in Section 9.0: Clinical Information Summary; Section 10.0: Preclinical Information Summary; and, Section 11.0: CMC Information Summary.

Following is the specific **question** for the Agency:

1 Does the Agency agree with the proposed NDA format and content plan described herein?

FDA RESPONSES:

Please see below responses from the following disciplines:

Clinical Pharmacology:

The sponsor's proposed NDA format and content plan appears acceptable from a clinical pharmacology perspective. However, the adequacy of the data to support the NDA will be a review issue.

Meeting Discussion:

No meeting discussion

Clinical:

Yes, however, your pivotal trial has its challenges. For example, the non-evaluable rate is 26.5% (69/260). Also, there were 16 patients at site #5, who were not randomized and were unblinded to the investigator for an additional non-evaluable rate of 6% (16/260). This is unacceptable for a pivotal trial. Whether this single randomized trial will be sufficient to support approval will be a review issue. As we previously mentioned to you, in order to support marketing approval, this single trial must be well designed, well conducted, internally consistent and provide statistically persuasive and clinically meaningful efficacy findings.

Meeting Discussion:

The sponsor clarified the reason for a relatively large percentage of patients that were non evaluable. This is expected with topical Nitrogen Mustard in Mycosis Fungoides because local reaction both of local toxicity and immune mediated occurs within the first three months. This is the first randomized trial of Nitrogen Mustard in Mycosis Fungoides and that captures the patient discontinuation rate more accurately than previous single arm trials. Moreover the patient's withdrawal rates are the same in both arms, and the non-inferiority margin is clearly met for both the ITT population and the evaluable population.

Chemistry Manufacturing and Controls:

Your proposed NDA format and content plan for module 3 appears acceptable.
At the time of NDA submission, our expectation is that you provide 12 months of real time stability data on 3 drug product registration batches under labeled storage conditions.

Meeting Discussion:

The Sponsor referenced the March 4, 2010 pre-NDA CMC meeting (question 7b) and asked if the (b) (4) expiration day period could be acceptable and supported by less than the requested amount of data. The Agency confirmed that this would be determined at the time of NDA filing. However, the Agency also acknowledged the Sponsor's intent to submit the NDA and accompanied stability package with a proposed (b) (4) expiration dating period.

Non-Clinical:

Your proposed NDA format and content plan for modules 2 and 4 appears acceptable.
The adequacy of published articles to support the NDA will be determined after the review of the articles.
Articles used to support sub-sections in modules 2 and 4 or to support non-clinical sections of the label should be linked to their corresponding sections.

Meeting Discussion:

No meeting discussion

Modupe Fagbami, RPM	**John R. Johnson, M.D., Meeting Chair**

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/s/

JOHN R JOHNSON
12/21/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 067839 **MEETING MINUTES**

Yaupon Therapeutics, Inc
Attention: Robert Alonso
President and CEO
259 N. Radnor-Chester Road
Suite 205
Radnor, PA 19087

Dear Mr. Alonso:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for nitrogen mustard (b) (4).

We also refer to the meeting between representatives of your firm and the FDA on March 4, 2010. The purpose of the meeting was to discuss Chemistry, Manufacturing and Controls Pre-NDA questions from your meeting briefing package.

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

If you have any questions, call Deborah Mesmer, Regulatory Project Manager at (301) 796-4023.

Sincerely,

{See appended electronic signature page}

Deborah M. Mesmer, M.S.
Regulatory Health Project Manager for Quality
Division of Pre-Marketing Assessment III and
Manufacturing Science
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure:

Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUG QUALITY ASSESSMENT

Sponsor Name:	Yaupon Therapeutics, Inc.
Application Number:	IND 067839
Product Name:	Nitrogen Mustard (b) (4)
Meeting Type:	Type B
Meeting Category:	Chemistry, Manufacturing and Controls, Pre-NDA
Meeting Date and Time:	Thursday, March 4, 2010, 13:00-14:00 ET
Meeting Location:	Food and Drug Administration, White Oak Campus, Silver Spring, MD
Received Briefing Package	February 2, 2010
Meeting Requestor:	Robert Alonso, President and CEO
Meeting Chair:	Richard Lostritto, Ph.D., Division Director, DPAMS, ONDQA
Meeting Recorder:	Deborah Mesmer, M.S.

FDA ATTENDEES:

CENTER FOR DRUG EVALUATION RESEARCH

Office of New Drug Quality Assessment

Deborah Mesmer, M.S., Regulatory Health Project Manager
Terrance Ocheltree, Ph.D., R.Ph. Pharmaceutical Assessment Lead
Richard T. Lostritto, Ph.D. Division Director, DPAMS, ONDQA
Anne Marie Russell, Ph.D. Review Chemist

Division of Drug Oncology Products

Haleh Saber, Ph.D., Pharmacology/Toxicology Supervisor
Alexander Putman, Ph.D., Pharmacologist

New Drug Microbiology Staff
Steven Fong, Ph.D., New Drug Microbiologist

EXTERNAL ATTENDEES:

Yaupon Therapeutics, Inc
Robert Alonso, President and CEO
Martin Stogniew, Ph.D., Chief Technology Officer
Philip Schein, M.D., Acting Chief Medical Officer (by phone)
Henry Mok, Ph.D., Director of Manufacturing/CMC
Jacqueline Yeager, Regulatory Affairs Associate
(b) (4) Regulatory Consultant
(b) (4) CMC Consultant

1.0 BACKGROUND

Nitrogen mustard (b) (4) 0.02% is being developed by Yaupon Therapeutics, Inc. (Yaupon) for the treatment of mycosis fungoides. A request for a Type B, CMC Pre-NDA meeting was submitted to the Office of Drug Oncology Products on November 30, 2010, and received on December 2, 2009. The meeting request was transferred to ONDQA, and a meeting was granted on December 16, 2009, for a face-to-face meeting to be held on March 4, 2010. The meeting briefing package dated February 1, 2010, was received on February 2. 2010. The purpose of meeting is to ensure that the type and amount of CMC data planned for inclusion in the NDA will be sufficient to support the submission. FDA preliminary responses were archived and shared with Yaupon on March 1, 2010, to promote an efficient discussion at the meeting held on March 4, 2010. Yaupon submitted via email from Ms. Jacqueline Yeager to Ms. Deborah Mesmer on March 3, 2010, responses to FDA preliminary responses and slides to present at the meeting. The minutes of the meeting discussion follow, with the March 3, 2010, responses from Yaupon inserted for clarity. The slides Yaupon presented are included as an attachment to these minutes.

2.0 SPONSOR QUESTIONS, FDA PRELIMINARY RESPONSES, AND MEETING DISCUSSION

2.1 MEETING INTRODUCTORY COMMENT

FDA stated that the Agency is not prepared to reach agreement on new questions posed in the Yaupon Responses submitted on March 3, 2010, in response to FDA's preliminary comments.

2.2 DRUG SUBSTANCE SUPPLY

Briefing Package Question 1 **Would the Agency accept a Letter of Authorization (b) (4) enabling Yaupon Therapeutics, Inc. (Yaupon) to cross reference the mechlorethamine HCl DMF (b) (4) in full satisfaction of the drug substance portions of Module 2 and Module 3 of the NDA to enable filing of the NDA?**

FDA Response to Question 1: No. In addition to the LOA, provide, at minimum, the following information in the drug substance portions of the NDA:

a. Nomenclature
b. Description
c. Molecular Structure, Molecular Weight and Molecular Formula
d. Physicochemical Properties
e. Specifications (Acceptance, Release and Stability) including Analytical Methods and Method Validation
f. Batch Analysis for the clinical supplies, registration batches and proposed to-be-marketed product
g. Stability Protocol and Stability Commitment
h. Stability Data

Yaupon's Response March 3, 2010- Request for Clarification on Question 1:
Yaupon is aware that the (b) (4) NM DMF# (b) (4) was reviewed by the Agency as part of an approved NDA Supplement in March 2009 for the Mustargen® (mechlorethamine hydrochloride) for Injection, 10 mg/vial NDA#06-695.

YT has obtained information from the "Open Portions" of DMF# (b) (4) and will provide all the requested information in the NDA, except for the Analytical Methods and Method Validation, which (b) (4) considers confidential. Thus, the LOA will enable access to this information and other confidential portions of the DMF.

Yaupong's Clarifying Question 1: **Will the Agency accept the NDA for filing based on the inclusion of the Open Portions of the DMF along with the DMF LOA?**

Considering the Mustargen supplement was recently approved, will the Agency accept the current tests and specifications included in the NM DMF for the YT application?

***Meeting Discussion*:** FDA stated at the outset of the meeting that the Agency was not prepared to reach agreement on new questions posed in Yaupon's clarifying questions.

Yaupon explained that the DMF holder considered analytical methods and methods validation confidential. In their absence, Yaupon proposed to provide acceptance test results for the first three lots of drug substance, conducted by a contract laboratory. FDA advised that this would not be sufficient and that acceptance testing must be:

- Conducted using a validated method
- Conducted on all lots of drug substance. No skip lot testing.
- Submitted in the NDA, as previously advised.

FDA advised that Yaupon could develop their own validated analytical method and bridge it to the DMF holder's Certificate of Analysis results. Alternately, Yaupon could obtain the analytical method from the DMF holder and qualify the transferred method by bridging their results to the Certificates of Analysis.

FDA also advised Yaupon to establish change controls with the DMF holder.
Reference: Yaupon Slide #4.

2.3 DRUG PRODUCT MANUFACTURING IN - PROCESS CONTROL (IPC)

Briefing Package Question 2: **Does the Agency agree that viscosity is a sufficient in-process control for the formulated bulk drug product?**

FDA Response to Question 2: No.

a. (b) (4) [redacted] in-process controls should also address quality concerns regarding bulk homogeneity and degradation of the API.

Yaupon's Response March 3, 2010- Request for Clarification on Question 2:

(b) (4) [redacted]

(b) (4) [redacted]

In order to address the Agency's request to control homogeneity of the bulk, YT proposes to implement the following. (b) (4) [redacted]

Homogeneity of the bulk (including purity/impurity measurements) will also be assessed (b) (4) [redacted]

***Yaupong's Clarifying Question 2*: Does the Agency find this approach acceptable to ensure homogeneity of the drug product?**

***Meeting Discussion*:** (b) (4) [redacted] FDA stated that the approach could be acceptable (b) (4) [redacted]

(b) (4)
FDA recommended that the quality data be included in the NDA.

FDA examined a placebo sample of the drug product presented by Yaupon at the meeting and stated that while it looked more like a gel (b) (4), the final determination is a review issue.

b. Pharmaceutical development should include studies to demonstrate control of parameters which affect quality during the manufacturing process (b) (4)

Yaupon's Response March 3, 2010: YT agrees and will develop the data to be provided in the NDA.

Meeting Discussion: There was no additional discussion at the meeting.

2.4 CONTROL TESTS – DRUG PRODUCT RELEASE AND STABILITY

Briefing Package Question 3a: **Does the Agency agree that the HPLC/UV content assay is sufficient to control the quality of the NM topical drug product at release and on stability at the recommended storage condition (b) (4)?**

FDA Response to Question 3a: No.

a. In addition to the proposed release and stability specifications for the drug product (appearance, pH, viscosity, assay and minimum fill), establish:
   i. a homogeneity specification to ensure uniform strength of the product in the as-marketed packages.
   ii. individual known, individual unknown, and total impurities specifications, (including related substances and degradants) to ensure purity.
   iii. a (b) (4) specification.
   iv. a (b) (4) specification (b) (4)
b. Develop an accurate analysis method and obtain reference standards for all impurities.
c. Establish the degradation pathway of your drug product and identify and report as per ICH all impurities, including degradants, in production and stability programs.
d. Report impurities based on the amount of the active pharmaceutical ingredient (b) (4) The meeting package reports (b) (4) impurities that have been observed, using a LC/MS method, in batches produced (b) (4) These impurities were reported (b) (4) When calculated as a percentage of the active pharmaceutical ingredient, these levels of impurity exceed ICH identification thresholds.
e. Conduct a temperature study to characterize the degradation profile under labeled use of the to-be-marketed product. The study data should be sufficiently robust to provide clear evidence to support the proposed expiry and evaluate worst case scenarios. (b) (4)

(b) (4)

f. As part of the stress evaluation of the drug product, conduct freeze/thaw studies.
g. Provide extractables/leachables data from studies conducted on the to-be-marketed products to demonstrate acceptable compatibility profiles for the container/closure systems.
h. As per your proposed dosing and administration instructions (e.g., "thin film") provide quantitative values of daily topical exposure of the API and all impurities which exceed ICH thresholds.
i. Modify the specifications to state that, if tested, the product will meet microbial limits testing criteria (b) (4) for total aerobic count and total yeast and mold, and be absent of pathogens (*hylococcus aureus*, *S. epidermidis*, *Pseudomonas aeruginosa*, *Bacillus subtilis*). The testing method should conform to the requirements in USP <61> and USP <62>.
j. See also FDA Response to Question 3b.

Yaupon's Response March 3, 2010- Request for Clarification on Question 3a:
YT would like to clarify a few points as shown below:

(a) YT agrees to develop proposed specifications for homogeneity, impurities, (b) (4) as requested by the Agency.

(b) YT has attempted to obtain reference standards for all impurities. As stated in the briefing book we have been unsuccessful to date. Two groups have attempted to produce reference standards. (b) (4) Both approaches have failed to produce reference standards. The details of these efforts will be included in the NDA.

YT will develop a procedure (b) (4) This approach will allow us to have a reproducible means of assessing the purity of the commercial material and ensuring that the commercial material is of an equal or higher purity than the clinical material.

***Yaupong's Clarifying Question 3*: Does the Agency agree with this approach?**

(c) YT agrees to establish the degradation pathway of the drug product and identify and report impurities according to ICH.

(d) YT agrees to report impurities based on the amount of the active pharmaceutical ingredient.

(e) YT agrees to perform a separate temperature cycling study and include the data in the NDA.

(f) YT agrees to perform Freeze/thaw studies and include the data in the NDA.

(g) YT will obtain and provide extractables/leachables information from the tube manufacturer and provide the information in the NDA.

(h) YT will provide quantitative values of daily topical exposure of the API and all impurities based on a total maximum daily dose of (b) (4) NM.

(i) YT agrees to evaluate the Microbial Limits specification based on the results of process validation batches to be made at UIP, and establish an appropriate testing scheme and specification.

Meeting Discussion: (b) (4) FDA advised that impurities and their levels need to be understood for the pharmacology/toxicology review, which will look at the amount the patient will receive and make a risk benefit assessment. FDA stated that impurities above the threshold defined in ICH Q3 should be qualified or their levels be justified. FDA advised Yaupon to provide tabulated information of impurities, their levels, and justification (based on non-clinical or clinical data) for those exceeding ICH levels.

Yaupon agreed to continue efforts to develop an accurate, quantitative analytical method, based on reference standards, to measure the drug product impurities and degradants. If the method developed is not based on reference standards, the FDA advised that close review of the method will be made and that Yaupon should clearly demonstrate how the method is robust and reproducible, employing a number of orthogonal analytical methods. FDA emphasized that (b) (4) the acceptability of the analytical methods will be a significant review issue.

Reference: Yaupon Slide #3

Briefing Package Question 3b: **Does the Agency agree** (b) (4)

FDA Response to Question 3b: No.

a. The submitted rationale (b) (4) is not acceptable (b) (4)

(b) (4)

b. See also FDA Response to Question 3a.

Yaupon's Response March 3, 2010- Request for Clarification on Question 3b: None requested.

Briefing Package Question 3c: **Does the Agency agree** (b) (4)

FDA Response to Question 3c: No. (b) (4) See also FDA Responses to Questions 3a and 3b.

Yaupon's Response March 3, 2010- Request for Clarification on Question 3c: None requested.

Question 4: **Does the Agency agree that MLT is not required for release or stability of the NM drug product?**

FDA Response to Question 4: Insufficient information was provided in your submission to determine if MLT is required for release or stability of the drug product. Provide summary data for MLT performed to date for all product batches. As advised in the Response to Question 3a, establish a microbial limits criterion in the drug product specification even if the product is demonstrated to have a low bioburden.

Yaupon's Response March 3, 2010- Request for Clarification on Question 4:
None requested. YT will provide the complete MLT testing data on all batches tested to-date, and agrees to establish appropriate microbial limits criteria in the drug product specification.

Question 5: **Does the Agency agree that Appearance, pH, Viscosity, Fill Weight and NM Content Assay are sufficient and adequate to control the quality of the drug product at release?**

FDA Response to Question 5: No. See FDA Response to Question 3a.

Yaupon's Response March 3, 2010- Request for Clarification on Question 5:
None requested.

2.5 MANUFACTURING PROCESS

Question 6: **Does the Agency agree that the information to be included in the NDA would be sufficient to support the filing of the NDA for drug product manufactured at UIP at a scale (b) (4) for both the (b) (4) and 60g tube fill weight?**

FDA Response to Question 6: A change of manufacturing site from clinical (b) (4) to commercial (UPI) (b) (4) raise a number of issues to address. Adequacy will be determined on review.

a. Demonstrate that the new site uses the same equipment, quality management systems, environmental conditions, drug product release specifications, controls in the manufacturing process, and that no changes have been made to the manufacturing batch records except for administrative information, location and language translation, where needed.
    i. Include a side-by-side comparison, in table format, of the two facilities and highlight changes, noting those that affect product quality.
    ii. Include batch analysis for at least three lots manufactured at each facility.
b. Demonstrate that the new site is Good Manufacturing Practices (GMP) compliant.
c. Demonstrate that the stability specifications implemented at the new UIP site are identical to those implemented at the (b) (4) site.
d. Provide complete stability data for both packages ((b) (4) and 60g) for all 3 registration lots manufactured at the commercial site.
e. Provide bridging studies to demonstrate equivalence between the product manufactured at the (b) (4) site and the UIP site, including side-by-side batch analysis comparison of individual lots. Match container size, formulation and all other quality parameters in the comparison analysis.

Refer to the following applicable guidance, "Guidance for Industry, Nonsterile Semisolid Dosage Forms" which is available electronically at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070930.pdf

Yaupon's Response March 3, 2010- Request for Clarification on Question 6:
The types of changes implemented during the process transfer (b) (4) to UIP were summarized on pages 0029-0032 in the CMC Meeting Briefing Document.
In accordance with the Guidance document referenced by the Agency, YT believes the process modifications would be considered (b) (4) as summarized in the table below.

(b) (4)

(b) (4)

(b) (4)

Modifications to the manufacturing batch records were required to accommodate these changes.

Overall, the changes were implemented (b) (4)

The first batch of drug product produced at UIP is being used in the pivotal clinical trial for the NDA submission. Two additional batches of drug product have since been produced at UIP and placed on stability.

Given that the (b) (4) UIP drug product is being used in the pivotal clinical trial, YT will provide the documentation required (b) (4) as defined in the referenced Guidance document. YT will also include the following:

- Bridging Data consisting of a side-by-side batch analysis comparison of individual lots.
- Stability data on the 3 UIP batches of drug product, along with the supportive stability data (b) (4)

Yaupon's Clarifying Question 6: **Does the Agency agree that this approach is sufficient to enable filing of the NDA?**

Meeting Discussion: (b) (4) FDA stated that for a bridging study, provide a complete run from each site. Yaupon agreed to provide a tabular comparison of the batch records from each site provided in the NDA.

2.6 STABILITY OF DRUG PRODUCT

Question 7a: **Does the Agency agree that the tests (Appearance, pH, Viscosity, and NM Content Assay) are sufficient to confirm the quality of the finished product during stability testing?**

FDA Response to Question 7a: No. See FDA Response to Question 3a

.

Yaupon's Response March 3, 2010- Request for Clarification on Question 7a:
None requested.

Question 7b: **Does the Agency agree that the stability package, including the number of lots, the amount of data, packaging configuration (tube not in unit carton) is sufficient to support filing the NDA and approvability of drug product manufactured at UIP in both the (b) (4) and 60g tube size?**

FDA Response to Question 7b:
a. It is recommended that at the time of submission, the NDA should contain at minimum – 12 months stability data for three registration lots of both package sizes manufactured at the UIP facility.
b. The stability tests and specifications should be the same as the release tests and specifications for all data submitted.
c. Any stability data from product manufactured at the clinical site (b) (4) will be supportive only and expiry will be based on the stability data submitted for the as-marketed product manufactured at the commercial site (UIP).

Yaupon's Response March 3, 2010- Request for Clarification on Question 7b:

a. As summarized in Table (3.2.P.8.1)2, page 0117 of the CMC Meeting Briefing Document (represented below for ease of reference with slight modification), the NDA will contain a minimum of 9 months of stability data for one UIP production[1] (registration) batch, and 6 months of data for 2 additional UIP production batches stored at the recommended storage condition (b) (4) These same lots are also being stored under accelerated conditions (25°C/60%RH) and the results from testing at 1, 2, 3 and 6 months will also be included in the NDA. All 3 lots have been prepared in both package sizes ((b) (4) and 60g).

It is important to note that all stability batches utilize the exact same formulation, and the first UIP production batch (b) (4) is also being used in the pivotal clinical study.

[1] In accordance with ICH Q1A(R2) Guidance on Stability of New Drug Substances and Products, **production batch** is defined as "A batch of a drug product manufactured at production scale by using production equipment in a production facility as specified in the application".

(b) (4)

[redacted]

b. As summarized in Table (3.2.P.5.1)1, page 0097 and Table (3.2.P.8.1)1, page 0116 of the CMC Meeting Briefing Document (and summarized here for ease of reference), the stability tests and specifications will be the same as the release tests and specifications for all data submitted. We have also included below the additional tests (impurities, uniformity/homogeneity, (b) (4) [redacted] and microbial limits) to be added as required by the Agency.

Test	Method	Release Testing Acceptance Criteria	Stability Testing Acceptance Criteria
Appearance	Visual	Clear to translucent	Clear to translucent
pH	USP <791>	2.5 – 4.5	2.5 – 4.5
Viscosity	USP <911>	(b) (4)	
Assay by HPLC	TM0008-005		
Impurities	TBD		
(b) (4)	TBD		
Uniformity (homogeneity)	TBD		
(b) (4) concentration	TBD		
Microbial Limits (if tested)	USP <61> and <62>		
Minimum Fill	USP <755>		

c. YT understands that the drug product commercial shelf life will be based on the real time data available from the long-term storage condition (b) (4) from the production batches produced at UIP. Periodic stability updates will be provided during the NDA review cycle.

Yaupon's Clarifying Question 7b: **Will the Agency accept the NDA for filing based on the amount of stability data described above that will be availability at the time of submission?**

Meeting Discussion: FDA reiterated that sufficient stability data to support a commercially viable shelf-life is needed at the time of filing and that (b) (4) stability data may be a filing issue;. Yaupon indicated that a (b) (4) shelf-life was commercially viable for their drug product (b) (4) FDA advised that Yaupon include a detailed justification in their application to support any shelf-life (b) (4)

(b) (4)
Yaupon committed to provide impurity measurements (b) (4)

Reference: Yaupon Slide #2

Question 7c: Does the Agency agree that photostability data do not need to be generated to support the planned NDA?

FDA Response to Question 7c: **No. Provide photostability studies as outlined in ICH Q1B.**

Yaupon's Response March 3, 2010: YT agrees to perform the required photostability studies and include the data in the NDA.

Meeting Discussion: There was no further discussion at the meeting.

2.7 DOSAGE FORM NOMENCLATURE

Question 8: **Does the Agency agree with the use of the term "gel" for the NM drug product dosage form?**

FDA Response to Question 8: Insufficient information was provided in the meeting package to make a determination of the drug product as (b) (4) gel. Based on the formulation information provided, (b) (4) the final determination will be made on NDA review. Provide a sample of the placebo product on NDA submission.

Yaupon's Response March 3, 2010- Request for Clarification on Question 8:
YT agrees to provide a sample of the placebo product upon NDA submission.

> ***Yaupon's Clarifying Question 8:*** **What additional information does the Agency need to enable a final decision on the dosage form nomenclature?**
> **Would the Agency provide instructions on how many samples are needed and where the samples should be sent?**

Meeting Discussion: See Meeting Discussion for Question 2.

2.8 ENVIRONMENTAL ASSESSMENT

Question 9: Does the Agency agree that the NM NDA would qualify for a categorical exclusion from the requirements to prepare an Environmental Assessment?

FDA Response to Question 9: This is a review issue.

Yaupon's Response March 3, 2010- Request for Clarification on Question 9:
In accordance with the FDA Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications (July 1998), YT believes that the NM NDA would qualify for categorical exclusion from the requirements to prepare an EA as described on page 0013 in the CMC Meeting Briefing Document.

> ***Yaupon's Clarifying Question 9:*** **Can the Agency provide clarification on where YT might obtain a reply on whether an EA is required, or if the Agency would accept a**

claim for categorical exclusion, so that YT can correctly prepare the NDA to be accepted for filing?

Meeting Discussion: FDA recommended that Yaupon include in their justification for exclusion that the drug product is an orphan drug at low concentration and is a cytotoxic agent. FDA committed to provide guidance regarding the ppm for environmental assessment as a post-meeting note in the meeting minutes.

Post-Meeting Note: Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications July 1998

2.9 NDA CMC FORMAT AND CONTENT PLAN

Question 10: Does the Agency agree with the proposed format and content plan for the CMC sections of the NDA?

FDA Response to Question 10:

a. Clearly identify the formulations (F1-F17) used in all studies (clinical, quality, non-clinical, etc) including the lot numbers, date of manufacture, manufacture info (batch size, site, etc), date of use, storage temperature, etc. Provide this information in a clear, easy-to-read table format.
b. See also FDA Response to Question 1.

Yaupon's Response March 3, 2010- Request for Clarification on Question 10:
None requested. YT wanted to clarify that the information presented in the Formulation Development section, Table (3.2.P.2.2.1)1 on page 0027 in the CMC Meeting Briefing Document, describes the early development work and did not result in batches that were used for any purpose. The NDA will include a comprehensive tabular summary of the requested information for all batches used in the pivotal clinical trial, as well as the stability batches.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further discussion at this time.

4.0 ACTION ITEMS

There are no specific due dates or time lines for submission of information or other action items. General agreements and commitments are included in the Meeting Discussion Section 2.0 above.

5.0 CONCURRENCE:

{See appended electronic signature page}

Deborah Mesmer
Regulatory Health Project Manager for Quality
Division of Pre-Marketing Assessment III and Manufacturing Science
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

{See appended electronic signature page}

Richard T. Lostritto, Ph.D.
Division Director
Division of Pre-Marketing Assessment III and Manufacturing Science
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

6.0 ATTACHMENTS AND HANDOUTS

As referenced in Section 1.0 Backgound, Yaupon submitted slides for the meeting by email. The slides are attached to these minutes.

7 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-67839	GI-1	YAUPON THERAPEUTICS INC	NITROGEN MUSTARD

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

/s/

DEBORAH M MESMER
05/10/2010

RICHARD T LOSTRITTO
05/10/2010

MEETING MINUTES

MEETING DATE: February 26, 2010 **TIME:** 3:00 pm

LOCATION: **WO** Building 22, Room 1309

IND: 067839

Meeting Request Submission Date: November 30, 2009

Briefing Document Submission Date: January 7, 2010

FDA Response Date: February 3, 2010

DRUG: Nitrogen Mustard (Mechlorethamine) (b) (4)

Sponsor: Yaupon Therapeutics Inc.

Type of Meeting: Type B Pre-NDA Non - Clinical Meeting (Teleconference)

INDICATION:

Treatment of Mycosis Fungoides

FDA PARTICIPANTS:

Robert Justice, M.D., Director, DDOP
Amna Ibrahim, M.D., Acting Deputy Director, DDOP
Haleh Saber, Ph.D., Pharmacology/Toxicology Supervisor, DDOP
Alex Putman, Ph.D., Pharmacology/Toxicology Reviewer, DDOP
Julie Bullock, Ph.D., Clinical Pharmacology Team Leader, DCP5
Frank Cross Jr., Chief, Project Management, Staff, DDOP
Modupe Fagbami, Regulatory Health Project Manager, DDOP

INDUSTRY PARTICIPANTS:

Robert Alonso, President and CEO
Martin Stogniew, Ph.D., Chief Technology Officer
Philip Schein, M.D., Acting Chief Medical Officer
Jacqueline Yeager, Regulatory Affairs Associate
(b) (4) Toxicology Consultant
(b) (4) Regulatory Affairs Consultant

BACKGROUND:

To discuss specific nonclinical issues related to the development of Nitrogen Mustard (NM) 0.02% (b) (4) to ensure that the type and amount of nonclinical data planned for inclusion in the NDA will be sufficient to support the submission.

1. Regulatory

Yaupon is planning to submit a 505(b)(2) New Drug Application for its proprietary formulation containing mechlorethamine hydrochloride; Mustargen® will be used as the Reference Listed Drug (RLD). Yaupon is proposing to accept the current labeling language which appears on the package insert for Mustargen® including Warnings for the use of the product (modified for the Yaupon topical product), Carcinogenesis, Mutagenesis, Impairment of Fertility, Usage in Pregnancy, and Pregnancy Category. Examples of the proposed language appear below.

"**WARNINGS**: This drug is **HIGHLY TOXIC** and the topical formulation must be handled and administered with care. Inhalation of dust or vapors and contact with skin or mucous membranes, especially those of the eyes, must be avoided. Avoid exposure during pregnancy. Due to the toxic properties of mechlorethamine (e.g., corrosivity, carcinogenicity, mutagenicity, teratogenicity), special handling procedures should be reviewed prior to handling and followed diligently."

"Usage in Pregnancy: Mechlorethamine hydrochloride can cause fetal harm when administered to a pregnant woman. MUSTARGEN has been shown to produce fetal malformations in the rat and ferret when given as single subcutaneous injections of 1 mg/kg (2-3 times the maximum recommended human dose). There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant."

"Carcinogenesis, Mutagenesis, Impairment of Fertility: Therapy with alkylating agents such as MUSTARGEN may be associated with an increased incidence of a second malignant tumor, especially when such therapy is combined with other antineoplastic agents or radiation therapy.

The International Agency for Research on Cancer has judged that mechlorethamine is a probable carcinogen in humans. This is supported by limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in animals. Young-adult female RF mice were injected intravenously with four doses of 2.4 mg/kg of mechlorethamine (0.1% solution) at 2-week intervals with observations for up to 2 years. An increased incidence of thymic lymphomas and pulmonary adenomas was observed. Painting mechlorethamine on the skin of mice for periods up to 33 weeks resulted in squamous cell tumors in 9 of 33 mice.

Mechlorethamine induced mutations in the Ames test, in *E. coli*, and *Neurospora crassa.* Mechlorethamine caused chromosome aberrations in a variety of plant and mammalian cells. Dominant lethal mutations were produced in ICR/Ha Swiss mice. Mechlorethamine impaired fertility in the rat at a daily dose of 500 mg/kg intravenously for two weeks."

"Pregnancy: Pregnancy Category D. See WARNINGS."
"Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from MUSTARGEN, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother."

Does the Agency agree that this approach is acceptable for the Yaupon product?

FDA Response:

Yes, from a non-clinical perspective, a 505(b)(2) application is an acceptable approach based on the information provided. You may rely on FDA's finding of non-clinical safety for a listed drug, as described in the drug approved labeling and/or rely on published literature for approval of your 505(b)(2) NDA. We will comment on the labeling language after submission of your NDA.

Clarification 1:

Does the Agency agree with the proposed format and content plan for the nonclinical sections of Module 2 and Module 4 of the NDA? [Please refer to Table 1 in our Request for Clarification document.]

Meeting Discussion:

The FDA stated that there are guidances available at the FDA site regarding the content and format of the NDA.

2. Systemic Toxicity

In an FDA communication dated 9 July 2004, the Agency indicated that systemic toxicity would only be required if there was evidence of systemic exposure. Yaupon is conducting a pivotal clinical trial in mycosis fungoides (MF) patients with its 0.02% Nitrogen Mustard (NM) formulation. Per agreement with FDA, blood samples were collected from both treatment arms for analysis of systemic NM levels (b) (4) The bioanalytical method utilized HPLC analysis with a limit of detection of 41.5 ng/mL. NM or half mustard (b) (4) levels were undetectable in all samples taken on Day 1 and after one month of exposure (n = 34, at

least 12 from the YT formulation). Yaupon is proposing that these data fulfill the Agency's request for this information.
Does the Agency agree that the data collected from the pivotal clinical study sufficiently demonstrate a lack of systemic exposure and no nonclinical toxicity or additional clinical studies are needed?

FDA Response:

It is unlikely that toxicology studies will be needed to assess systemic toxicities associated with mechlorethamine. However, a final decision will be made after review of data submitted with your NDA. In addition, the adequacy of the pharmacokinetic study and validation of the bioanalytical assays will be a review issue.

Clarification 2:

Does the Agency agree that submission of the bioanalytical report along with the bioanalytical method and method qualification report, all of which will be included in Module 5, Section 5.3.1 will support filing of the NDA?

Meeting Discussion:

The Agency agrees that the sponsor's plan is acceptable.

3. Genetic and Reproductive Toxicity

A large database of information is available in the nonclinical published literature on the genetic toxicity and reproductive toxicity of nitrogen mustard. NM is mutagenic and has been shown to produce malformations in mice and rats. Yaupon is proposing that these data are sufficient to address these two endpoints and to fulfill the Agency's request for this information.
Does the Agency agree that no additional nonclinical genetic toxicity or reproductive toxicity studies are needed?

FDA Response:

Considering nitrogen mustard is a known mutagen and teratogen, we agree that no additional nonclinical genetic toxicity or reproductive toxicity studies are needed. Additionally, for a 505(b)(2) NDA, you may rely on FDA's finding of non-clinical safety for a listed drug, as described in the drug approved labeling; see our response to Question 1.

4. Carcinogenicity

The potential of topically applied NM to produce secondary tumors has been evaluated in the published clinical literature. The clinical literature suggests a possibility for

developing only secondary cutaneous tumors. Yaupon is proposing that, based on the available clinical literature, the risk for secondary tumors has been evaluated fulfilling the Agency's request for this information. In addition, under the SPA, Yaupon is conducting a 12-month surveillance of patients that were involved in the pivotal clinical trial monitoring them for the development of potential secondary tumors. Separately, Yaupon and the clinical investigators are planning to conduct an extension protocol to continue following patients for up to five years to monitor the development of secondary tumors. Data from the 12-month surveillance and the 5-year extended follow up will be submitted in safety updates and NDA Annual Reports.

Does the Agency agree that **no nonclinical or additional clinical studies are needed** to address the potential risk for developing secondary tumors?

FDA Response:

Yes.

5. Dermal Toxicity

As part of the pivotal clinical trial, Yaupon has collected information on the dermal effects (reported as treatment limiting toxicities, TLTs) of the Yaupon 0.02% NM formulation. These dermal effects are consistent with reported effects of other ointment formulations of topical NM products (Kim 2003). Yaupon is proposing that these data provide the specific information on the formulation that FDA has requested.

Does the Agency agree that no nonclinical studies are needed to address the dermal effects of Yaupon's proprietary 0.02% NM and that sufficient information has been and is being collected from Yaupon's clinical program?

FDA Response:

Based on minimal information provided, we cannot comment on the adequacy of your assessment of dermal effects of your drug product. A final decision will be made after review of data submitted with the NDA.

Clarification 5:

Does the Agency agree that no nonclinical studies are needed to address the dermal effects of YT's drug product to enable filing of the NDA?

Meeting Discussion:

It is unlikely that the lack of nonclinical dermal study(ies) will be a filing issue.

6. Repeat-Dose Toxicity

With respect to repeat dosing, effects of the 0.02% NM formulation in patients are available along with data from the published clinical literature (Kim et al. 2003). Based on this database of information, Yaupon is proposing that the safety of NM and Yaupon's proprietary formulation has been adequately addressed via the published literature and the pivotal clinical trial.
Does the Agency agree that the information described herein is sufficient and that no nonclinical studies are required?

FDA Response:

See our responses to Questions 1, 2, and 5.

Clarification 6:

Does the Agency agree that the published literature may be used to populate the nonclinical toxicology sections of the product labeling; and, that the results from the clinical study will dictate the safety profile for the drug product?

Meeting Discussion:

FDA reiterated that published literature may be used to populate the nonclinical toxicology sections.

7. Toxicity (b) (4)

(b) (4) Yaupon believes that the nonclinical as well as the clinical data provide adequate information on potential topical and systemic effects of this component and that there are no safety concerns.

Does the Agency agree that the information described herein, including the emerging clinical database from Yaupon's pivotal trial, is sufficient and that no additional toxicology studies are needed (b) (4)?

FDA Response:

Based on minimal information provided, we cannot comment on the qualification (b) (4) **Qualification could be based on nonclinical or clinical data. We recommend that a tabulated summary be provided in your NDA** (b) (4)

(b) (4)

Clarification 7:

Does the provided Table 2 satisfy the general type and amount of information the Agency requires to meet the request? [Please refer to Table 2 in our Request for Clarification document.]

Meeting Discussion:

The type of information provided is generally acceptable. The adequacy of information will be a review issue. (b) (4)

8. Phototoxicity

Nitrogen mustard has been evaluated for potential absorption in the UV range (290 to 700 nm). No absorption was observed in this range. Based on these data and FDA's Guidance for Industry entitled "Photosafety Testing", Yaupon proposes that no phototoxicity studies are needed.

Does the Agency agree that no phototoxicity studies are needed?

FDA Response:

Your proposal appears acceptable. A final decision will be made after review of data submitted with the NDA. Please see ICH S9 (Nonclinical Evaluation for Anticancer Pharmaceuticals; http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129110.pdf)

Clarification 8:

Would the Agency please clarify the use of a reference to the ICH S9 Guideline relative to the possible requirements for phototoxicity? Does the Agency agree that a phototoxicity study is not required to enable filing of the NDA?

Meeting Discussion:

It is unlikely that the lack of photosafety study(ies) will be a filing issue. In addition, based on the data presented, photosafety studies are generally not needed.

Modupe Fagbami, RPM **Haleh Saber, Ph.D. Meeting Chair**

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-67839	GI-1	YAUPON THERAPEUTICS INC	NITROGEN MUSTARD

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

/s/

HALEH SABER
03/01/2010