

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-393

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-393

SUPPL #

HFD # 150

Trade Name ISTODAX

Generic Name romidepsin

Applicant Name Gloucester Pharmaceuticals, Inc.

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(1)

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

YES NO

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

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

d) Did the applicant request exclusivity?

YES NO

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

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

YES NO

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

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA#

NDA#

NDA#

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

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

summary for that investigation.

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

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

YES NO

If yes, explain:

Name of person completing form: Lisa Skarupa
Title: Regulatory Project Manager
Date: October 15, 2009

Name of Office/Division Director signing form: Robert L. Justice, M.D., M.S.
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

LISA M SKARUPA
10/21/2009

ROBERT L JUSTICE
10/21/2009

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-393

Supplement Number:

NDA Supplement Type (e.g. SE5):

Division Name: DDOP

PDUFA Goal Date:

Stamp Date: January 12, 2009

November 12, 2009

Proprietary Name: ISTODAX

Established/Generic Name: romidepsin

Dosage Form: for Injection, 10mg per single use vial

Applicant/Sponsor: Gloucester Pharmaceuticals, Inc.

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: ISTODAX is a histone deacetylase (HDAC) inhibitor indicated for treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy.

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)
- (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 ^Δ	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

- 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
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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).

Additional pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

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
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	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

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

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?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

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:

Lisa Skarupa, RPM

Regulatory Project Manager

(Revised: 6/2008)

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



Gloucester
PHARMACEUTICALS

Gloucester Pharmaceuticals, Inc.

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December 11, 2008

Robert Justice, MD
Director, Division of Oncology Drug Products
FDA, CDER
5901-B Ammendale Road
Beltsville, MD 20705

**RE: NDA 22-393 – Original Application
Debarment Certification**

Dear Dr. Justice:

Gloucester Pharmaceuticals, 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.

Sincerely yours,

Jean Nichols, Ph.D.
President & Chief Operating Officer

Attachment B: Sample 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.

PMR 1556-1
Description: Conduct a GLP embryo-fetal developmental reproductive toxicology study in rats to assess the embryo-fetal toxicity of romidepsin. The results from the rat study will determine if a study in a second species is warranted.

PMR/PMC Schedule Milestones: Final protocol Submission Date: 07/31/2010
Study/Clinical trial Completion Date: 11/30/2010
Final Report Submission Date: 06/30/2011
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC 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

Due to the life-threatening condition of the patient population and the benefit:risk consideration, the study will be conducted as a PMR .

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."

The embryofetal developmental toxicity study submitted with the NDA was inadequate. The goal of the PMR study is to adequately assess the risk (e.g. teratogenicity or lethality) to a developing embryo/fetus resulting from the administration of ISTODAX .

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.

A GLP embryo-fetal developmental reproductive toxicology study in rats to assess the embryo-fetal toxicity of romidepsin. The results from the rat study will determine if a study in a second species is warranted.

Required

- Observational pharmacoepidemiologic study
 Registry studies

Continuation of Question 4

- 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
 - 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?

- 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?

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.

(signature line for BLAs)

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.

An animal study(ies) to determine the estrogenic/anti-estrogenic effects of romidepsin.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- 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
 - 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?

- 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?

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.

(signature line for BLAs)

Attachment B: Sample 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.

PMR 1556-3
Description: Conduct a GLP toxicology study in an appropriate animal species to characterize the toxicity profile of _____ The data from this study will be used in the justification of the acceptance criterion for _____ in romidepsin drug product administered IV on Days 1, 8 and 15 of a 28-day cycle.

b(4)

PMR/PMC Schedule Milestones: Final protocol Submission Date: 06/30/2010
Study/Clinical trial Completion Date: 09/30/2010
Final Report Submission Date: 02/28/2011
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC 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

The final ISTODAX drug product contains the _____ Considering that the toxicity profile of I.V. administered _____ has not been adequately characterized and this _____ may have contributed to adverse reactions observed in patients in clinical trials, the applicant needs to assess the toxicity profile of I.V. administered _____ in nonclinical study(ies). The specification of _____ per 10 mg romidepsin vial is currently acceptable for the marketing of the drug, based on available clinical data and the benefit:risk consideration for this life-threatening indication. The PMR study will identify the toxicity profile of I.V. administered _____

b(4)

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."

The final ISTODAX drug product contains the _____ This _____ is not currently listed in ICH Q3C, and the safety of IV administered _____ has not been adequately established. This _____ will be present at up to _____ in the drug product and may contribute to toxicities associated with ISTODAX. Adverse reactions reported in patients treated with ISTODAX suggest that some of the toxicities may have been associated with _____ The goal of the PMR study is to characterize toxicities associated with IV administered _____ in an appropriate animal species and to justify the acceptance criterion for _____ 1 in ISTODAX drug product administered IV on Days 1, 8 and 15 of a 28-day cycle.

b(4)

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.

A GLP toxicology study will be conducted in an appropriate animal species to characterize the toxicity profile of: _____

b(4)

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- 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
 - 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?

- 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?

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.

(signature line for BLAs)

Attachment B: Sample 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.

PMR 1556-4
Description: Conduct an *in vitro* induction study using cryopreserved human hepatocytes to evaluate the effects of romidepsin on the 3 inducible forms of cytochrome P450 (CYP1A2, CYP3B6 and CYP3A4).

PMR/PMC Schedule Milestones: Final protocol Submission Date: 04/30/2010
Study/Clinical trial Completion Date: 07/31/2010
Final Report Submission Date: 10/31/2010
Other: _____ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC 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

The NDA review indicates a need for an *in vitro* study as no information regarding the induction potential of romidepsin on the activity of CYP enzymes was submitted in the application.

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.”

An *in vitro* study is needed to assess whether or not romidepsin is an inducer of major CYP enzymes. This will provide information on whether romidepsin will decrease the concentrations of drugs metabolized by these enzymes, which can be a serious risk. Depending on the outcome, an *in vivo* drug-drug interaction trial may be warranted.

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.

The study will be an in vitro assessment using cryopreserved human hepatocytes to evaluate the effects of romidepsin on CYP1A2, CYP3B6 and CYP3A4.

Required

- Observational pharmacoepidemiologic study
 Registry studies

Continuation of Question 4

- 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
 - 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?

- 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?

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.

(signature line for BLAs)

Attachment B: Sample 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.

PMR 1556-5 Description: Conduct a drug interaction clinical trial with a CYP3A4 inhibitor, ketoconazole, in patients with advanced cancer. This trial will be a crossover design to evaluate the effects of ketoconazole on the pharmacokinetic disposition of romidepsin.

PMR/PMC Schedule Milestones: Final protocol Submission Date: 07/31/2010
Study/Clinical trial Completion Date: 07/31/2012
Final Report Submission Date: 12/31/2012
Other: _____ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC 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

PK evaluation during NDA review indicated the need for an *in vivo* study. Romidepsin is extensively metabolized by CYP3A4 in human liver microsomes *in vitro*. Thus, co-administration of romidepsin with strong CYP3A4 inhibitors can lead to increase in romidepsin concentrations and risk of toxicity. However, no clinical drug-drug interaction trail has been conducted to address this issue. Therefore, a drug interaction clinical trial with a strong CYP3A4 inhibitor, such as ketoconazole, is required.

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.”

Romidepsin is extensively metabolized by CYP3A4. Therefore, co-administration of romidepsin with strong CYP3A4 inhibitors can lead to increase in romidepsin concentrations and risk of toxicity. A clinical trial with a strong CYP3A4 inhibitor, such as ketoconazole, is needed to accurately determine the magnitude of romidepsin exposure changes when they are co-administered. Depending on the results, a safe dose of romidepsin will be identified when co-administered with strong CYP3A4 inhibitors.

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.

The required drug-drug interaction clinical trial will be a phase 1, crossover design to evaluate the effect of a CYP3A4 inhibitor, ketoconazole, on the pharmacokinetics of romidepsin.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- 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
 - 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?

- 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?

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.

(signature line for BLAs)

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.

The required drug-drug interaction clinical trial will be a phase 1, crossover design to evaluate the effects of a CYP3A4 inducer, rifampin, on the pharmacokinetics of romidepsin.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- 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
 - 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?

- 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?

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.

(signature line for BLAs)

Attachment B: Sample 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.

PMR 1556-7
Description: Conduct a clinical trial to determine the pharmacokinetics of romidepsin in advanced cancer patients with moderate and severe hepatic impairment. Submit the protocol for agency review prior to commencing the trial.

PMR/PMC Schedule Milestones: Final protocol Submission Date: 08/31/2010
Study/Clinical trial Completion Date: 08/31/2014
Final Report Submission Date: 08/31/2015
Other: _____ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC 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

PK evaluation during NDA review indicated the need for a clinical trial in patients with moderate and severe hepatic impairment. In the NDA submission, the Applicant employed a population PK approach using data from 3 clinical trials to evaluate the effect of hepatic impairment on the PK of romidepsin. The results indicate that mild hepatic impairment does not alter the PK of romidepsin. There seems to be a trend of increased romidepsin concentrations in the two patients with moderate hepatic impairment compared to that of the patients with normal liver functions. However, due to the limited number subjects with moderate hepatic impairment and the absence of subjects with severe hepatic impairment in the dataset submitted, the effect of moderate and severe hepatic impairment on the PK of romidepsin is unknown.

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."

Romidepsin is metabolized in the liver. Therefore, moderate and severe hepatic impairment may result in increased romidepsin concentrations and lead to serious risk. A trial in patients with moderate and severe hepatic impairment is required in order to identify safe doses for patients with moderate or severe hepatic impairment.

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.

The required clinical trial will be a phase 1 trial designed to assess the PK of romidepsin in advanced cancer patients with moderate and severe hepatic impairment. The Applicant will submit the protocol for agency review prior to commencing the trial.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- 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
 - 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?

- 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?

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.

(signature line for BLAs)

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.

GPI-06-0005 is an ongoing, open-label, single-arm, exploratory phase 1 study that is being conducted at a single study center in the US in patients with advanced malignancies. Intensive PK sampling and ECG monitoring are occurring in the study. Based on the results from the study, the effect of romidepsin on QT prolongation will be determined.

Required

- Observational pharmacoepidemiologic study
 Registry studies

Continuation of Question 4

- 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
 - 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)
QT prolongation assessment using non-thorough QT study design.
-

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?

- 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?

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.

(signature line for BLAs)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22393	ORIG-1	GLOUCESTER PHARMACEUTICA LS INC	ROMIDEPSIN FOR INFUSION

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/s/

SUSAN JENNEY
11/04/2009

SUSAN K CUMMINS
11/04/2009

From: Skarupa, Lisa
Sent: Wednesday, November 04, 2009 9:06 AM
To: 'Joan Shankle'; Denise Hayes; Monika Witczak
Cc: Cross Jr, Frank H
Subject: RE: Additional change to labeling NDA 22393

Good morning,

We approve the 36 month expiry

Sincerely,
Lisa

From: Joan Shankle [mailto:joan.shankle@gloucesterpharma.com]
Sent: Thursday, October 29, 2009 11:20 AM
To: Skarupa, Lisa; Denise Hayes; Monika Witczak
Cc: Cross Jr, Frank H
Subject: RE: Additional change to labeling NDA 22393

Hello Lisa

Thank you for the summary.

How and when do we receive notification of approved expiry? We submitted a 3-year expiry in NDA and the manufacturing team needs this information for production planning and labeling operation.

Best regards,
Joan

MEMORANDUM OF TELECON

DATE: October 14, 2009

APPLICATION NUMBER: NDA 22,393

BETWEEN:

Applicant: Gloucester Pharmaceuticals, Inc

Phone: 1-866-866-2244

AND

Division of Drug Oncology Products

Gloucester Pharmaceuticals, Inc.

Jean Nichols, Ph.D., President & Chief Operating Officer

Denise Hayes, Sr. Director, Regulatory & Quality

Joan Shankle, NDA Project Manager

William McCulloch, MB, FRCP, Senior Medical Advisor

CJ Godfrey, Ph.D., Pharmacometrics

Christopher H. Cabell, MD MHS FACC, Cardiologist

FDA

Robert Justice, M.D., Director, DDOP

Anthony Murgo, M.D., Deputy Director, DDOP

Virginia E. Maher, M.D., Clinical Team Leader, DDOP

Qin Ryan, M.D., Clinical Reviewer, DDOP

Kun He, Ph.D., Biostatistics Team Leader, OTS/OB/DBV

Huanyu Chen, Ph.D., Biostatistics Reviewer, OTS/OB/DBV

Haleh Saber, Ph.D., PharmTox Team Leader, DDOP

Todd Palmby, Ph.D., PharmTox Reviewer, DDOP

Alexander Putman, Ph.D., PharmTox Reviewer, DDOP

Qi Liu, Ph.D., Clinical Pharmacology Team Leader, DCP5

Hua Lillian Zhang, Ph.D. Clinical Pharmacology Reviewer, DCP5

Nitin Mehrotra, Ph.D. Clinical Pharmacology Reviewer, DCP5

Christine Garnett, Ph.D., Reviewer from QT-Interdisciplinary Review Team

SUBJECT: Discussion on the proposed Post Marketing Requirements.

The Applicant requested a telecon with the Agency to discuss the PMRs sent to them on September 30, 2009. Of the eight PMRs, the Applicant requested to focus on two areas:

1. The cardiac assessment report in the original NDA submission included an analysis of ECG matched PK data for 7 patients from Study GPI-06-0005 in patients with advanced solid tumors. Per our pre-NDA agreement, we have continued to collect ECG matched PK data in our ongoing clinical trials. In Study GPI-06-0005 in patients with advanced solid tumors, ECG matched PK data has been collected for an additional 24 patients; 15 patients administered 14 mg/m² of romidepsin as a 4-hour infusion and 9 patients (3 at 8 mg/m² and 6 at 12 mg/m²) administered romidepsin as a 1-hour infusion. Our proposal to determine the potential of ISTODAX to prolong QT is to repeat the exposure-response analysis provided in the NDA using the expanded dataset from Study GPI-06-0005, (N=31). We would like to discuss this approach with the FDA review team.

Meeting Discussion: The Applicant's approach is acceptable. The Applicant agrees to submit the reanalysis for the exposure response, central tendency, and outlier analysis for the Study GPI-06-0005. Whether these data will fulfill the PMR will be a review issue. Please use only observed Concentration-ECG data from study GPI-06-0005 for exposure-response analysis.

2. Gloucester believes that the analyses in the original NDA submission show that mild and moderate hepatic impairment had no clinically important effect on romidepsin disposition. Additional justification is provided in the response to the DDOP labeling changes of 6 October 2009 (attached to this email for your convenience). Based on this, we propose to conduct a study only in patients with severe hepatic impairment and we would like to discuss this approach with the FDA review team.

Meeting Discussion: The number of patients with moderate hepatic impairment N=2 is not adequate to support the Applicant's claim that moderate hepatic impairment does not alter the pharmacokinetics of romidepsin, so clinical trial to determine the PK of romidepsin in patients with moderate and severe hepatic impairment is needed. The Applicant can conduct this study in cancer patients other than CTCL patients. The Agency suggests that the Applicant submit the study protocol for FDA review prior to starting the study.

The Applicant's attached the following background information regarding hepatic impairment:

Effect of Hepatic Impairment

Gloucester believes that the analyses in the original NDA submission show that mild and moderate hepatic impairment had no clinically important effect on romidepsin disposition. An integrated population pharmacokinetic (PK) approach was used to assess the impact of altered hepatic function on the PK of romidepsin (Report AN10022). In addition, PPK modeling was combined with the rigor of replication stability, which enables determination of the importance of a selected covariate beyond the dataset analyzed to the population at large, to assess impact of moderate hepatic impairment (see AN10022, Section 6.3.6.3.2.1).

The National Cancer Institute (NCI) Organ Dysfunction Working Group (NCI ODWG) liver function classification was used to categorize subjects, in terms of liver function, who contributed pharmacokinetic (PK) data in studies (1312, FJ-228-0001, GPI-06-0005). There were 15 subjects with mild hepatic impairment, and 2 subjects with moderate hepatic impairment in the dataset, the rest of the subjects (i.e. 128) in the dataset had normal hepatic function.

The primary objective of a hepatic impairment study is to determine, based on the behavior of a drug in patients with normal liver function, whether the PK of the drug is altered in patients with hepatic impairment to the extent that an adjustment to the dosage would be indicated. To do this it is necessary to have a control group derived from the intended patient population (with apparently normal hepatic function), and not from young, healthy volunteers. To the extent possible, the control group should be similar to patients with respect to age, weight, and gender. It is for this reason that the PPK approach for characterizing the effect of hepatic impairment on drug disposition was used to investigate the effect of hepatic impairment on romidepsin disposition.

Recognizing the fact that there were two subjects who had moderate hepatic impairment, 15 with mild hepatic impairment and 128 with normal hepatic function, the characterization of the effect of hepatic impairment was performed using two approaches – a percentile division coupled with a randomization test approach using the full data set, and a PPK modeling combined with a knowledge creation (simulation) approach using a subset of the data [see AN10022 Sections 6.3.5.2 to 6.3.6.3.1, 7.7, and 8 (3rd paragraph from the end of the discussion section)].

The percentile division approach coupled with randomization test clearly demonstrated that moderate hepatic impairment as well as mild hepatic impairment did not significantly affect the disposition of romidepsin (see AN10022, Section 7.7). A similar finding was obtained using the PPK modeling combined with a knowledge creation (simulation) approach (see AN10022, Section 7.7).

It is worthy to note that in determining the effect of moderate hepatic impairment on romidepsin clearance, advantage was taken of the fact that the two subjects with moderate hepatic impairment had romidepsin clearance values that were on average 33% lower than subjects with normal or mildly impaired hepatic function. Based on this, virtual subjects were generated using intersubject variability and covariate distribution similar to those observed for subjects with normal or mildly impaired hepatic function

The results of this investigation showed that moderate hepatic impairment had no significant effect on romidepsin disposition, therefore no dosage adjustment is required for this group of subjects [see AN10022, Section 8 (3rd paragraph from the end of the discussion section)].

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ORIG-1

GLOUCESTER
PHARMACEUTICA
LS INC

ROMIDEPSIN FOR INFUSION

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/s/

QI LIU
10/27/2009

VIRGINIA E MAHER
10/29/2009

MEMORANDUM OF TELECON

DATE: October 13, 2009

APPLICATION NUMBER: NDA 22,393

BETWEEN:

Applicant: Gloucester Pharmaceuticals, Inc

Phone: 1-866-866-2244

AND

Division of Drug Oncology Products

Gloucester Pharmaceuticals, Inc.

Jean Nichols, Ph.D., President & Chief Operating Officer

Denise Hayes, Sr. Director, Regulatory & Quality

Joan Shankle, NDA Project Manager

Nicholas Vrolijk, Ph.D., Sr. Vice President Manufacturing Operations

Darrell Nix, Ph.D., Sr. Director, Drug Development

John Balsler, PhD, Sr. Biostatistician

FDA

Robert Justice, M.D., Director, DDOP

Anthony Murgo, M.D., Deputy Director, DDOP

Virginia E. Maher, M.D., Clinical Team Leader, DDOP

Qin Ryan, M.D., Clinical Reviewer, DDOP

Kun He, Ph.D., Biostatistics Team Leader, OTS/OB/DBV

Huanyu Chen, Ph.D., Biostatistics Reviewer, OTS/OB/DBV

Richard Lostritto, Ph.D., Division Director, OPS/ONDQA/DPAMS

John Leighton, Ph.D., DABT, Associate Director for Pharmacology/Toxicology, OODP

Haleh Saber, Ph.D., PharmTox Team Leader, DDOP

Todd Palmby, Ph.D., PharmTox Reviewer, DDOP

Alexander Putman, Ph.D., PharmTox Reviewer, DDOP

Qi Liu, Ph.D., Clinical Pharmacology Team Leader, DCP5

Hua Lillian Zhang, Ph.D. Clinical Pharmacology Reviewer, DCP5

SUBJECT: Discussion on the Pharmacology/Toxicology Deficiency

On September 28, 2009, FDA sent the Pharmacology/Toxicology Deficiency to the Applicant.

“For safety reasons, the level of _____ in the drug product may not exceed _____ per 10 mg romidepsin vial. This is based on patient exposure during clinical trials and a maximum proposed dose of 14 mg/m². Provide revised drug product specifications which include a limit on _____ to not exceed _____ per 10 mg romidepsin vial.”

b(4)

On October 5, 2009, the Applicant submitted their response to the Pharmacology/Toxicology Deficiency.

“Gloucester’s response to the Pharmacology/Toxicology Deficiency notification provided in your email on 28 September 2009 is attached. In this response Gloucester is providing information on patient exposure during clinical trials of romidepsin at doses that are higher than the maximum proposed dose of 14 mg/m². Data from these trials were included in the assessment of safety in NDA 22-393.

Gloucester is proposing to revise the drug product specifications to include a limit for _____ per 10 mg romidepsin vial. This limit is supported by patient exposure in clinical trials of romidepsin and the risk evaluation provided in our earlier submission related to the justification of the _____ limit.

b(4)

If the DDOP reviewers do not concur with the proposed specification after reviewing this additional information, Gloucester is requesting a teleconference with the Pharmacology/Toxicology and CMC reviewers to discuss the data provided to DDOP related to the justification of the _____ limit and in the context the post marketing requirement to characterize toxicities associated with I.V. administered _____.

b(4)

A teleconference to discuss the Pharmacology/Toxicology Deficiency was scheduled on October 13, 2009. On October 9, 2009, FDA sent the items for discussion based on the Applicant's response.

The purpose of the teleconference will be to discuss the following:

b(4)

- 1) The highest dose (mg) of romidepsin and _____ given to patients with CTCL in the GPI study.
- 2) Describe the AE profile for 20 patients who received the highest dose (mg) of _____ . Please compare these AEs to the AEs of patients who received lower doses of _____. Please limit your analysis to patients who received at least 3 cycles of romidepsin.
- 3) Provide convincing data to indicate that doses higher than _____ will not significantly add to toxicities associated with romidepsin. For example an intra-patient analysis which compares the AE profile following administration of study product with a small amount (such as a batch containing _____ per vial) of _____ and the AE profile following administration of study product with a larger amount (e.g., batch containing _____ per vial) of _____.
- 4) Please provide the dataset for all the above analysis.

b(4)

b(4)

MEETING DISCUSSION: A teleconference was held to discuss the specifications for a _____ in romidepsin drug product. FDA stated that data provided on October 5, 2009 do not adequately justify the proposed _____ specification of _____ per 10 mg vial, mainly for the following reasons: the number of patients who received romidepsin doses (on a mg basis) higher than those administered to CTCL patients in the GPI study is small; some patients were exposed to only one dose or 2 doses of romidepsin; and it is not clear what dose of _____ was delivered to these patients, as it appeared that multiple vials with different levels of _____ were used during the study. The Applicant could either keep the specification at _____ /10 mg vial or provide a detailed analysis of adverse reactions in a substantial number of patients who received different doses of _____.

b(4)

The Applicant will consider their options and if they choose to conduct a detailed analysis of adverse events they will provide a timeline for the analysis.

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NDA-22393	ORIG-1	GLOUCESTER PHARMACEUTICA LS INC	ROMIDEPSIN FOR INFUSION

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/s/

HALEH SABER
10/16/2009

VIRGINIA E MAHER
10/16/2009

From: Skarupa, Lisa
Sent: Thursday, October 15, 2009 11:53 AM
To: 'Denise Hayes'
Subject: IR October 15 2009 NDA 22393

Dear Denise,

Please explain why the two USUBJID, which were in the datasets of the original NDA, was not included in the safety update datasets.

USUBJID_OF_AAE

402 GPI-04-0001-32043
924 GPI-04-0001-56079

Please let me know if you have any questions. Let me know when is the earliest you can send this to us?

Lisa

From: Skarupa, Lisa
To: "Denise Hayes";
Subject: IR October 15 2009 NDA 22393
Date: Thursday, October 15, 2009 11:53:03 AM

Dear Denise,

Please explain why the two USUBJID, which were in the datasets of the original NDA, was not included in the safety update datasets.

USUBJID_OF_AAE

402 GPI-04-0001-32043
924 GPI-04-0001-56079

Please let me know if you have any questions. Let me know when is the earliest you can send this to us?

Lisa

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/s/

LISA M SKARUPA
10/15/2009

From: Skarupa, Lisa
Sent: Friday, October 09, 2009 4:29 PM
To: 'Denise Hayes'
Cc: Joan Shankle; Cross Jr, Frank H
Subject: Teleconference FDA-Gloucester October 13

Good afternoon Denise,
The purpose of the teleconference will be to discuss the following:

- 1) The highest dose (mg) of romidepsin and _____ given to patients with CTCL in the GPI study. b(4)
- 2) Describe the AE profile for 20 patients who received the highest dose (mg) of _____ Please compare these AEs to the AEs of patients who received lower doses of _____ Please limit your analysis to patients who received at least 3 cycles of romidepsin. b(4)
- 3) Provide convincing data to indicate that doses higher than _____ will not significantly add to toxicities associated with romidepsin. For example an intra-patient analysis which compares the AE profile following administration of study product with a small amount (such as a batch containing _____ per vial) of _____ and the AE profile following administration of study product with a larger amount (e.g., batch containing _____ per vial) of _____ b(4)
- 4) Please provide the dataset for all the above analysis.

Sincerely,

Lisa

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

From: Denise Hayes [<mailto:denise.hayes@gloucesterpharma.com>]
Sent: Tuesday, October 06, 2009 7:12 PM
To: Skarupa, Lisa
Cc: Joan Shankle
Subject: RE: pharmtox deficiency

Thanks Lisa. I will keep an eye out for the information what the focus of the meeting should be.

Here is the telecon information.

Dial in: 1-866-866-2244
International dial in: 1 404 260 1415
Participant Code: 5266394
Host: Denise Hayes

Take care,
Denise

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ORIG-1

GLOUCESTER
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LS INC

ROMIDEPSIN FOR INFUSION

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/s/

LISA M SKARUPA
10/09/2009

From: Skarupa, Lisa
To: "Denise Hayes";
cc: Cross Jr, Frank H;
Subject: NDA 22-393 for ISTODAX: Timeline for PMRs
Date: Wednesday, September 30, 2009 3:01:28 PM

Denise,

Please refer to your NDA 22-393 for romidepsin. We need you to provide actual date (that is the final protocol submission, study completion, and submission of the final report submission) for the following Post-Marketing Requirements:

1. The reproductive toxicology studies conducted in rats did not result in significant maternal or embryo-fetal toxicity, and are therefore deemed inadequate to assess potential risk to a developing embryo or fetus associated with romidepsin treatment. Adequate embryo-fetal risk assessment should be provided. Embryo-fetal toxicology studies are typically conducted in two species. If romidepsin causes embryo-fetal lethality or is teratogenic in one species, a study in the second species may not be warranted. Provide dates for final protocol submission, study completion, and submission of the final report submission.

2. Romidepsin was shown to bind to estrogen receptors *in vitro*. Toxicology studies suggested romidepsin modulation of estrogen signaling as evidenced by female-specific findings (e.g. atrophy of mammary gland, uterus, ovary and vagina; pituitary hyperplasia; elevated cholesterol and triglycerides). Therefore, romidepsin may increase the risk of estrogen-agonist-like serious risks, such as uterine cancer, clotting, and cardiovascular disease, or the risk of estrogen-antagonist-like serious risks, such as osteoporosis and fracture. In addition, romidepsin may interfere with hormonal contraceptives, resulting in high-risk pregnancies. Please assess estrogenic and anti-estrogenic effects of romidepsin. The assessment could be based on clinical or non-clinical data. Provide dates for final protocol submission, study or clinical trial completion, and submission of the final report submission.

3. The final ISTODAX drug product contains the _____
_____ This : _____ is not currently listed in ICH Q3C, and the safety of I.V. administered _____ has not been adequately established. The amount of _____ delivered to patients in clinical trials was _____ of the dose of your drug product, and may have contributed to toxicities seen in clinical trials. Characterize toxicities associated with I.V. administered : _____ in at least one non-clinical toxicology study, using an appropriate animal species,

b(4)

and propose a safe clinical dose based on your data. Provide dates for final protocol submission, study completion, and submission of the final report submission.

4. Conduct a drug interaction trial to evaluate the effect of CYP3A4 inhibitor (e.g. ketoconazole) on the pharmacokinetics of romidepsin. Provide dates for final protocol submission, trial completion, and submission of the final report submission.

5. Conduct a drug interaction trial to evaluate the effect of CYP3A4 inducer (e.g. rifampin) on the pharmacokinetics of romidepsin. Provide dates for final protocol submission, trial completion, and submission of the final report submission.

6. Conduct a trial to determine the pharmacokinetics of romidepsin in patients with moderate and severe hepatic impairment. Provide dates for final protocol submission, trial completion, and submission of the final report submission.

7. Perform a trial to determine the potential of ISTODAX to prolong QT. Provide dates for final protocol submission, trial completion, and submission of the final report submission.

8. Conduct an *in vitro* study to determine whether romidepsin is an inducer of CYP enzymes including CYP3A4. Provide dates for final protocol submission, study completion, and submission of the final report submission.

Let me know if you have any questions.

Sincerely,
Lisa

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ORIG-1

GLOUCESTER
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LS INC

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/s/

LISA M SKARUPA
09/30/2009

From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Monday, September 28, 2009 3:28 PM
To: Denise Hayes
Subject: IR Sept 28 2009

Denise,
I need this as soon as possible.

Please provide a list of batch ID numbers by time (month and year) of use for NCI study and GPI study. Also provide a list of patient ID numbers by year of use in the NCI study.

Thanks,
Lisa

Application
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/s/

LISA M SKARUPA
09/28/2009

From: Skarupa, Lisa
To: "Denise Hayes";
cc: Cross Jr, Frank H;
Subject: PharmTox Deficiency Sept 28 2009
Date: Monday, September 28, 2009 4:21:54 PM

Hello Denise

Please forward to your team the following PharmTox Deficiency that needs to be addressed as soon as possible:

For safety reasons, the level of _____ in the drug product may not exceed _____ per 10 mg romidepsin vial. This is based on patient exposure during clinical trials and a maximum proposed dose of 14mg/m2. Provide revised drug product specifications which include a limit on _____ to not exceed _____ per 10 mg romidepsin vial.

b(4)

Sincerely,
Lisa

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NDA-22393

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GLOUCESTER
PHARMACEUTICA
LS INC

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/s/

LISA M SKARUPA
09/28/2009

From: Mesmer, Deborah
Sent: Thursday, September 24, 2009 4:51 PM
To: 'Denise Hayes'
Cc: Jean Nichols
Subject: NDA 22-393: FDA advice correspondence 09/24/09

From: Deborah Mesmer, Project Manager for Quality, CDER/ONDQA/DPAMS

To: Jean Nichols, PhD., President and Chief Operating Officer, Gloucester Pharmaceuticals, Inc.
Cc: Denise Hayes, Sr. Director, Regulatory & Quality, Gloucester Pharmaceuticals, Inc.

Please refer to your New Drug Application, NDA 22-393, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ISTODAX (romidepsin) for injection.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comment in response to the email inquiry from Ms. Denise Hayes dated August 17, 2009, to Ms. Deborah Mesmer:

Please refer to your August 26, 2009, amendment, which was a response to the FDA IR letter dated August 10, 2009. In your response to comment 2, you acknowledge FDA's recommendation that you conduct _____ study using _____. Your proposals to share your study plan prior to the next campaign and to conduct the study during the next campaign are acceptable.

b(4)

FDA/CDER
Office of New Drug Quality Assessment
Division of Pre-Marketing Assessment III and Manufacturing Science

From: Denise Hayes [mailto:denise.hayes@gloucesterpharma.com]
Sent: Monday, August 17, 2009 8:03 PM
To: Mesmer, Deborah
Cc: Jean Nichols
Subject: RE: Authorization for Courtesy Copy of Communication (NDA 22-393)

Dear Debbie:

I am writing in regards to the information request for NDA 22-393 that you sent to Jean Nichols on 12 August 2009. The Gloucester team is requested clarification on the following:

We have noted the recommendation that Gloucester conduct a _____ study with _____ to demonstrate the capability of the assay method to detect diastereomers as an extension of the data provided in the NDA per the agreement at the Pre-

b(4)

NDA CMC Meeting of 30 May 2007. We wish to clarify expectations regarding execution of this study with regard to NDA review. This year's romidepsin drug substance production campaign was completed in July 2009. We plan to develop an _____ and plan to share this with FDA prior to the next production campaign. Will this approach allow the FDA CMC reviewers to continue to evaluate the NDA for potential approval?

b(4)

We would appreciate receiving a response as soon as possible to allow us to incorporate the information in the response that you have requested we send to you by Monday 24 August 2009.

Best regards,

Denise

Denise Hayes
Sr. Director, Regulatory & Quality
Gloucester Pharmaceuticals, Inc.
One Broadway, 14th Floor
Cambridge MA 02142 USA
Telephone: 617-583-1356
Fax: 617-401-3614
Email:Denise.Hayes@Gloucesterpharma.com

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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NDA-22393	ORIG-1	GLOUCESTER PHARMACEUTICALS INC	ROMIDEPSIN FOR INFUSION
NDA-22393	ORIG-1	GLOUCESTER PHARMACEUTICALS INC	ROMIDEPSIN FOR INFUSION

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/s/

DEBORAH M MESMER
09/25/2009

From: Skarupa, Lisa
To: "Denise Hayes";
cc: Cross Jr, Frank H;
Subject: RE: NDA 22393 Labeling first version Sept 18 2009
Date: Monday, September 21, 2009 9:08:47 AM

Denise,
Please update the tables in the label based on the data from 120th-day update, Sept 17th submission.

Please let me know that you received this, thank you.

Lisa

From: Skarupa, Lisa
Sent: Friday, September 18, 2009 6:38 PM
To: Denise Hayes
Cc: Cross Jr, Frank H
Subject: NDA 22393 Labeling first version Sept 18 2009

Good afternoon Denise,

Please see the attached changes to the Labeling for NDA 22393.
We are planning to send the PMC/PMR early next week.
<< File: NDA 22393 Romidepsin Label version9182009.doc >>

Thank you,
Lisa

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NDA-22393	ORIG-1	GLOUCESTER PHARMACEUTICA LS INC	ROMIDEPSIN FOR INFUSION

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/s/

LISA M SKARUPA
09/21/2009

From: Skarupa, Lisa
Sent: Monday, September 14, 2009 12:26 PM
To: 'Denise Hayes'; Joan Shankle
Subject: Sept 14 2009 IR datasets

Good afternoon,

Thank you for taking time to communicate with the FDA review team. We would like to have the following information by noon Sep 15, 2009 for finalizing the label.

1. Please submit a clarification and/or explanation of the discrepancies between the data sets AAE and AKEY, including:
 - a. A list of the studies with more than one study ID
 - b. A list of studies IDs and titles that were excluded from AKEY
2. Please update your 120-day safety update datasets to ensure that only one USUBJID and one study ID is included per subject.
3. Please update the tables in your 120-day safety update report (submitted on May 15, 2009) as necessary. We realize that this will require considerable effort. Please submit an update to tables 1, 7, 8, 10, 11, and 12 by Sep 15, 2009 for finalizing the label. This can be followed by an update of the remainder of the tables by Sep 17, 2009.

Sincerely,
Lisa
301-796-2219

From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Monday, September 28, 2009 3:28 PM
To: Denise Hayes
Subject: IR Sept 28 2009

Denise,

Please provide a list of batch ID numbers by time (month and year) of use for NCI study and GPI study. Also provide a list of patient ID numbers by year of use in the NCI study.

Thanks,
Lisa

From: Skarupa, Lisa
Sent: Wednesday, September 09, 2009 12:10 PM
To: 'Denise Hayes'
Subject: Romidepsin IR Sept 9 2009

Hello Denise,

Please specify that among 131 patients of the NCI 1312 study in your safety update data set, how many were CTCL and how many were PTCL.

Lisa

From: Skarupa, Lisa
Sent: Wednesday, September 09, 2009 3:18 PM
To: 'Denise Hayes'
Subject: RE: Romidepsin IR Sept 9 2009 part 2

Good afternoon Denise,

Please see the second piece to the IR sent this morning. Clinical and Stats, as I stated on my voicemail message, would like to just Set up a tcon to help them locate the data sets. Available in the morning from 10am-12 or Monday 10am or after 2pm.

Please verify the summary below and explain the O category in NCI study 1312 Index from the safety update AKEY data set.

Data set	AAE		AKEY	
	No. of Studies	No. Pt with AE	No. of Studies	Pt No.
Total	38	897	34	872
CTCL	2	183	2	185
	GPI-04-0001	100	GPI-04-0001	102
	NCI 1312	83	NCI 1312	83
	NCI 1312 C+P	122 (39 Pts)	NCI 1312 C+P+O	131 (9 Os)
Other tumors	36	714	32	587



NDA 22-393

INFORMATION REQUEST

Gloucester Pharmaceuticals, Inc.
Attention: Jean Nichols, Ph.D.
President & Chief Operating Officer
One Broadway, 14th Floor
Cambridge, MA 02142

Dear Dr. Nichols:

Please refer to your new drug application (NDA) dated January 12, 2009, received January 12, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for ISTODAX (romidepsin) for infusion.

We are reviewing the Istodax diluent container labels, container label and carton labeling submitted February 18, 2009. We have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

A. Diluent Container Label

We recommend you revise the following features to provide distinction between the diluent vial and the active drug vial:

1. Increase the prominence of the word 'Diluent' on the diluent container label. Post-marketing experience with intravenous products that have a separate diluent requiring reconstitution has shown that medication errors have occurred involving inadvertent use of the diluent instead of the drug during administration. Providing increased prominence of the word 'Diluent' on the container label may serve to avert confusion such as this during drug preparation and administration of Istodax.
2. Present the word 'Diluent' on a separate line from the proprietary name and use a larger, bolded font size to present the word 'Diluent'.
3. Delete the established name and decrease the prominence of the proprietary name 'Istodax' on the principal display panel of the diluent container label to minimize the potential that the diluent will be mistaken for the active drug.
4. Revise the presentation of the proprietary name 'Istodax' so it is not presented with the same trade dress as it is presented on the drug vial. This will also serve to help distinguish the active drug vial from the diluent vial.

5. Add quantitative and/or qualitative information regarding the inactive ingredients Propylene Glycol and Dehydrated Alcohol where they appear on the principal display panel of the diluent container label per 21 CFR 201.100 (b)(5).
6. Revise the presentation of "Inactive Ingredient" to read "Each vial contains" on the principal display panel of the diluent container label.
7. Revise the language accompanying "Dosage and Administration" on the principal display panel of the diluent container label to provide additional emphasis on the need to reconstitute Istodax with the accompanying Diluent. Delete the language "~~_____~~
~~_____~~ and replace it with "Withdraw 2 mL of diluent for use to reconstitute 10 mg vial of Istodax."

b(4)

B. Container Label and Carton Labeling

1. Add the final concentration after reconstitution (5 mg/mL) to principal display panel of container label and carton labeling below the strength (10 mg). For example: After reconstitution with 2 mL of Diluent, the final concentration of Istodax is 5 mg/mL. This information should be displayed on the principal display panel of carton labeling and if space permits, it should also be displayed on the principal display panel of the container label.
2. Consider revising the reconstitution and dilution statement on the bottom of the principal display panel of the container label and the side panel of the carton labeling to include reference to the volume of diluent to be added (2 mL of). This may provide clarity to providers calculating the concentration and dose when preparing the drug for administration. We recommend the statement be revised to read: Product **MUST** be reconstituted with **2 mL of** supplied diluent and then further diluted in 0.9 % Sodium Chloride Injection, USP.
3. Revise the presentation of the dosage form 'For Reconstitution' on container labels to the CDER Dosage Form "For Injection" and add the dosage form "For Injection" after the established name on the carton labeling.
4. Revise the presentation of the strength (10 mg) on the principal display panel of the container label and the carton labeling to read "10 mg per vial" to provide clarity regarding product strength.
5. Add a statement after the language "Single-use vial" on the container label and carton labeling such as "Discard Unused Portion" to provide emphasis in the product being single-use only.
6. Given the limited space available on the Istodax container label, we recommend deleting the statement
~~_____~~

b(4)

b(4)

7. Since the Istodax carton contains the diluent and the active ingredient for preparing the drug for administration, add the word 'Kit' to the upper section of the principal display panel of the carton labeling above the proprietary name.

8. Add information regarding the components packaged in the Istodax carton to the principal display panel of the carton labeling. We recommend the following:

Each carton contains:

1 single-use vial containing 10 mg of Istodax

1 vial containing 2 mL of Diluent

9. Revise the statement which appears on the principal display panel of the carton labeling that reads "MUST BE RECONSTITUTED AND DILUTED PRIOR TO ADMINISTRATION" to include "WITH ENCLOSED DILUENT" and relocate to directly below the strength (10 mg per vial). We recommend the added language to provide emphasis on the need to use the diluent included in the packaging to reconstitute the product before administration.

If you have any questions, call me at (301) 796-2219.

Sincerely,

{See appended electronic signature page}

Lisa Skarupa, R.N., M.S.N., A.O.C.N.
Regulatory Project Manager
OND/OODP
Division of Drug Oncology Products

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22393	ORIG-1	GLOUCESTER PHARMACEUTICALS INC	ROMIDEPSIN FOR INFUSION
NDA-22393	ORIG-1	GLOUCESTER PHARMACEUTICALS INC	ROMIDEPSIN FOR INFUSION

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

/s/

LISA M SKARUPA
09/04/2009



NDA 22-393

INFORMATION REQUEST LETTER

Gloucester Pharmaceuticals, Inc.
Attention: Jean Nichols, Ph.D.
President and Chief Operating Officer
One Broadway, 14th Floor
Cambridge, MA 02142

Dear Dr. Nichols:

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

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request your written response by August 24, 2009, in order to continue our evaluation of your NDA.

1. Provide physical and chemical properties of these forms, including their solubilities in various **b(4)**
2. We have reviewed your peak purity study results for romidepsin and its forced degradation samples. However, detection of diastereomers in a forced degradation sample is unlikely if the reference sample does not also contain diastereomers. Therefore, this study does not confirm that the method is capable of detecting such diastereomers. We recommend that you perform a _____ study with the _____ and using a reference romidepsin sample to demonstrate the capability of your analytical method for the detection of diastereomers.
3. The total impurity levels in your clinical batches and validation batches for drug substance were _____ or lower. Revise your proposed acceptance criterion of _____ for total impurities in the drug substance to more closely reflect batch experience or provide further justification. **b(4)**
4. Your proposed reconstitution time of _____ appears much longer than the validation batch data _____ indicate. Revise it to more closely reflect batch experience or provide additional justification. **b(4)**
5. Total impurity levels in the drug product were _____ or lower in all batches. Revise your proposed acceptance criterion _____ for total impurities in the drug product to reflect batch experience or provide further justification. **b(4)**

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

Sincerely,

{See appended electronic signature page}

Sarah Pope Miksinski, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

Sarah Pope Miksinski
08/10/2009

From: Skarupa, Lisa
Sent: Wednesday, August 05, 2009 5:37 PM
To: 'Denise Hayes'
Subject: NDA 22393 IR August 5th ClinPharm

Good afternoon Denise,

ClinPharm's Information Request to be requested by August 11:

In the DRUG INTERACTIONS of HIGHLIGHTS OF PRESCRIBING INFORMATION, you states that

⌞ Please provide detailed information (e.g., doses and timing of ISTODAX and the anticoagulants, name of the anticoagulants, PT and INR values, demographic information of the patient, pharmacokinetic data if available) , or locate the information source (e.g., study number and the report location in the submission) by August 11, 2009.

b(4)

Thank you,
Lisa

From: Skarupa, Lisa
Sent: Thursday, August 13, 2009 4:18 PM
To: 'Denise Hayes'
Subject: Romidepsin IR August 13

Good afternoon Denise,

1. When would you be able to send the datasets for your safety update?

2. When will you be responding to the question about progressive disease?

GPI-04-0001 required progression to be confirmed by a second report of progression. In calculating the duration of responses we have used the first date of progression. However, there may be patients who had one report of progression that was not confirmed by a second report of progression. Please send us a dataset containing all reports of progression and the dates of progression.

Thank you,
Lisa

From: Skarupa, Lisa
Sent: Tuesday, August 04, 2009 7:06 PM
To: 'Denise Hayes'
Subject: IR for August 4 romidepsin

Hi Denise,

Information Request August 4th:
Romidepsin

1. Patients GPI-04-0001-54-049, GPI-04-0001-94-083, and GPI-04-0001-52-061 discontinued due to an allergic reaction (per investigator). We note that this was not included in the draft PI. Please provide your rationale.
2. Please provide additional information on the following events. We are particularly interested in whether any of these were ventricular tachycardia or torsades.
5270-3701517
5270-3814658
5270-3939844
6319-71103016
6325-907600092
6338-00695118
6338-695118
GPI-06-0003-01029
T95-0077-31-02-15-4
6325-900430526
6325-907692101
3. GPI-04-0001 requires confirmation of PD in patients with CR or PR. Did you include all patients with PD in your datasets or did you limit this to patients with confirmed PD? If the datasets were limited to patients with confirmed PD, please provide a dataset with the patient ID, time of first CR or PR, all assessments of PD, and the time of each assessment.

Please acknowledge receipt and confirm possible times for response.

Thank you

Lisa

From: Skarupa, Lisa
Sent: Wednesday, July 29, 2009 11:24 AM
To: 'Denise Hayes'
Subject: NDA 22393 IR July 29 clinical

Denise,

Clinical would like to know the following: please provide case report forms for all patients who died or discontinued study drug on NCI 1312?

Please let us know how soon would you be able to send this information.

Thanks,

Lisa

From: Skarupa, Lisa
Sent: Tuesday, July 28, 2009 7:57 AM
To: 'Denise Hayes'
Subject: July 28 IR for statistician calculation of DURDR

Good morning Denise,

Please clarify your algorithm on the duration of investigator assessment response (for CR and PR), ASAP. If there are other datasets used in the calculation of the DURDR, please provide detailed information such as datasets and all variables used.

As you stated in both variable label and define.pdf for dataset ain.v.xpt, DURDR is the duration of ODR (object disease response, CR or PR), which is equal to (progdt - first resp). FDA statistician could not find a variable named first response date. Instead, it was comment for variable ERESPDT. In addition, all of the PROGDTs were missing when one or both of the best investigator response date or the earliest response date were available. Please see details in the data attached below.

Based on proc contents, the agent found below variable definitions:

10	DURDR	Num	8		Duration of ODR (progdt - first resp)
20	ERESPDT	Num	8	DATE9.	Earliest Response Date (define.pdf comment: Date of first response)
19	BRESPDT	Num	8	DATE9.	Best Response Date
28	PROGDT	Num	8	DATE9.	Progression date

All the records for responder (CR, CRp) in AINV.

Obs	USUBJID	PROGDT	ERESPDT	BESTR_C	BRESPDT	DURDR
4	GPI-04-0001-02004	.	24AUG2005	CCR	.	568
5	GPI-04-0001-02022	.	03JAN2006	PR	29NOV2005	260
9	GPI-04-0001-02035	.	21FEB2006	PR	21FEB2006	57
14	GPI-04-0001-03008	.	31AUG2005	PR	31AUG2005	64
17	GPI-04-0001-04005	.	22JUL2005	PR	15JUL2005	134
22	GPI-04-0001-23067	.	22FEB2007	PR	22FEB2007	170
25	GPI-04-0001-28090	.	11SEP2007	PR	11SEP2007	101
30	GPI-04-0001-31021	.	02DEC2005	PR	02DEC2005	61
32	GPI-04-0001-32038	.	23MAR2006	PR	23MAR2006	57
33	GPI-04-0001-32043	.	21NOV2006	PR	21NOV2006	108
35	GPI-04-0001-33028	.	08FEB2006	PR	08FEB2006	155
38	GPI-04-0001-34014	.	07SEP2005	PR	07SEP2005	217
40	GPI-04-0001-35026	.	17FEB2006	PR	17FEB2006	454
42	GPI-04-0001-35032	.	10MAR2006	PR	10MAR2006	238
43	GPI-04-0001-36020	.	16DEC2005	CCR	22FEB2006	153
48	GPI-04-0001-37018	.	08DEC2005	CCR	02MAR2006	141
49	GPI-04-0001-38033	.	20FEB2006	PR	.	1
50	GPI-04-0001-38074	.	17MAY2007	CCR	17MAY2007	43
53	GPI-04-0001-45072	.	10APR2007	PR	10APR2007	246
55	GPI-04-0001-45095	.	16AUG2007	PR	11OCT2007	260
57	GPI-04-0001-46088	.	23JUL2007	PR	23JUL2007	281
58	GPI-04-0001-46094	.	27AUG2007	PR	27AUG2007	253
61	GPI-04-0001-47062	.	08JAN2007	PR	08JAN2007	73
63	GPI-04-0001-48039	.	03MAY2006	PR	03MAY2006	169
66	GPI-04-0001-48044	.	09AUG2006	PR	09AUG2006	603
67	GPI-04-0001-48060	.	03JAN2007	CCR	28FEB2007	141
68	GPI-04-0001-48086	.	13JUN2007	PR	05SEP2007	85
69	GPI-04-0001-51055	.	27DEC2006	PR	27DEC2006	274
75	GPI-04-0001-52065	.	10MAY2007	PR	10MAY2007	280
79	GPI-04-0001-55069	.	04APR2007	PR	04APR2007	30
85	GPI-04-0001-81076	.	25JUN2007	PR	25JUN2007	86
88	GPI-04-0001-92089	.	24OCT2007	CCR	24OCT2007	50
91	GPI-04-0001-94080	.	26JUN2007	PR	26JUN2007	58

98	NCI1312-34-34-48-5	.	.	PR	.	1953
100	NCI1312-35-54-80-6	.	.	CCR	.	2002
103	NCI1312-36-00-75-0	.	.	CCR	.	1785
104	NCI1312-36-21-45-5	28AUG2002	.	PR	.	140
105	NCI1312-36-26-18-0	04JUN2003	.	PR	.	420
109	NCI1312-36-77-68-0	11FEB2004	.	CCR	.	336
111	NCI1312-37-27-53-1	26JAN2004	.	PR	.	299
118	NCI1312-38-55-93-4	28SEP2004	.	PR	.	223
119	NCI1312-38-89-88-9	20OCT2004	.	PR	.	147
120	NCI1312-39-11-21-4	.	.	PR	.	889
124	NCI1312-40-38-57-5	.	.	PR	.	224
137	NCI1312-900-00-3880	.	.	PR	.	190
138	NCI1312-900-00-4262	.	.	PR	.	622
139	NCI1312-900-00-4757	.	.	PR	.	197
143	NCI1312-900-00-4892	19JUL2005	.	PR	.	49
144	NCI1312-900-00-4919	28JUN2005	.	PR	.	49
145	NCI1312-900-00-4932	14SEP2005	.	PR	.	148
148	NCI1312-900-00-4986	08AUG2005	.	PR	.	80
149	NCI1312-900-00-5023	.	.	PR	.	35
150	NCI1312-900-00-5027	13JUL2005	.	PR	.	56
153	NCI1312-900-00-5103	.	.	PR	.	56
154	NCI1312-900-00-5124	29NOV2005	.	PR	.	56
156	NCI1312-900-00-5141	.	.	CCR	.	363
157	NCI1312-900-00-5228	.	.	PR	.	379
159	NCI1312-900-00-5344	.	.		.	

Thanks,
Lisa

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (*Division/Office*) Maternal Health Team Consult, Tammie Howard

FROM: HFD-150/ Lisa Skarupa

DATE
July 23, 2009

IND NO.

NDA NO.
22-393

TYPE OF DOCUMENT
electronic

DATE OF DOCUMENT
January 12, 2009

NAME OF DRUG:
romidepsin (ISTODAX)

PRIORITY
CONSIDERATION

CLASSIFICATION OF DRUG
NME

DESIRED COMPLETION DATE
30 days

NAME OF SPONSOR: Gloucester Pharma

REASON FOR REQUEST

I. GENERAL

NEW PROTOCOL

PROGRESS REPORT
NEW CORRESPONDENCE
DRUG ADVERTISING
ADVERSE REACTION REPORT
MANUFACTURING CHANGE/ADDITION
MEETING PLANNED BY

PRE-NDA MEETING

END OF PHASE II MEETING
RESUBMISSION
SAFETY/EFFICACY
PAPER NDA
CONTROL SUPPLEMENT

RESPONSE TO DEFICIENCY LETTER (fax)

FINAL PRINTED LABELING
LABELING REVISION
ORIGINAL NEW CORRESPONDENCE
FORMULATIVE REVIEW
OTHER (*SPECIFY BELOW*) **NEW NDA**

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

TYPE A OR B NDA REVIEW
END OF PHASE II MEETING
CONTROLLED STUDIES
PROTOCOL REVIEW
OTHER

STATISTICAL APPLICATION BRANCH

CHEMISTRY REVIEW
PHARMACOLOGY
BIOPHARMACEUTICS
OTHER

III. BIOPHARMACEUTICS

DISSOLUTION
BIOAVAILABILITY STUDIES
PHASE IV STUDIES

DEFICIENCY LETTER RESPONSE
PROTOCOL-BIOPHARMACEUTICS
IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
DRUG USE e.g. POPULATION EXPOSURE,
ASSOCIATED DIAGNOSES
CASE REPORTS OF SPECIFIC REACTIONS (*List below*)
COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

REVIEW OF MARKETING EXPERIENCE, DRUG USE AND
SAFETY
SUMMARY OF ADVERSE EXPERIENCE
POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please see attached request.

MO= Qin Ryan, PharmTox = Todd Palmby (Haleh Saber TL), ClinPharm Lillian Hua Zhang (Qi Liu TL)

Label to send in the email. Applicant sent it via eDR, here is the link: \\CDSESUB1\EVSPROD\NDA022393\0000

SIGNATURE OF REQUESTER
Lisa Skarupa

METHOD OF DELIVERY (*Check one*)
 FAX

electronic

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

To Maternal Health Team:

We would like a consultation regarding the Pharmacology/Toxicology review and labeling for NDA 22393 (Istodax). Our discussion will focus on the following two issues:

- 1) The sponsor submitted a study in rats to address the effects of romidepsin when administered to pregnant females during the period of organogenesis. We determined this study to be inadequate, and the risk to a developing fetus remains unknown. This is a cytotoxic drug (histone deacetylase inhibitor) and based on the mechanism of action has potential to impact embryofetal development. We have included a summary of the data for this inadequate study in section 8.1 of the PLR label. We will likely be requesting a PMR for completing an adequate study addressing the effect of this drug on a developing fetus. We would like your input with the following question:

Do you agree that the language included in sections 5.5 and 8.1 of the proposed label for Istodax provide sufficient information on the potential risk to a fetus for a pregnant woman taking this drug given that the non-clinical data is inadequate at this time?

- 2) There is evidence that romidepsin may bind to estrogen receptors. An *in vitro* binding assay determined that romidepsin competes with β -estradiol for binding to estrogen receptors at concentrations that could be comparable to drug plasma levels achievable in patients receiving the clinical dose. There is no further characterization of the pharmacology of romidepsin binding to estrogen receptors (i.e. whether it may activate or inhibit the receptors is unknown), or the effect of this binding on estrogen levels or responses in animals. However, results of non-clinical toxicology studies in rats included atrophy of the mammary gland, ovary, uterus and vagina, pituitary hyperplasia and elevated cholesterol and triglyceride levels in female rats at significantly lower plasma levels compared to the human levels after receiving the clinical dose. Our main concern at this time is the potential for romidepsin to interfere with the efficacy of oral hormone contraceptive drugs, especially since the label is warning physicians and patients about the risk of becoming pregnant while taking Istodax. It is likely these contraceptive methods will be employed to prevent pregnancy. We would like your input with the following question:

Should information regarding the potential for romidepsin to interfere with the effectiveness of oral hormone contraceptive drugs be included in the label at this time? If so, please recommend appropriate language and location for such information.

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

/s/

Lisa M Skarupa
7/23/2009 01:11:46 PM

From: Skarupa, Lisa
Sent: Wednesday, July 22, 2009 11:42 AM
To: 'Denise Hayes'
Subject: STATS IR July 22, 2009 NDA 22393

Good morning Denise,

FDA statistical reviewer took a look at SAS program C-conmed.sas and c_maingpinci, and could not locate some datasets and macro (setup.sas) used in the program. Those datasets were not reported in P2's table on response to sensitivity analyses request for 19 June 2009 .pdf . If the datasets were submitted, please provide a list and locations for those raw and derived datasets (a hyperlink will be very helpful and appreciated). At this time, FDA statistical reviewer could not review the results submitted dated on July 14. For future submission, e-mail to RPM is the fastest way but please also submit to EDR.

Sincerely,

Lisa

From: Skarupa, Lisa
Sent: Tuesday, July 14, 2009 8:56 AM
To: 'Denise Hayes'
Subject: Information Request July 14 2009 NDA 22393
Importance: High

Regarding your Justification of Specifications of the Drug Product (eCTD module 3.2.P.5.6.5) and the acceptance criterion for _____, we have the following comment and information requests:

b(4)

- 1) We are not familiar with the 1/10000 LD50 approach based on the referenced published article (Conine 1992) for estimation of a safe level of _____. Multiple references and recommendations (including that from NIOSH) are available that provide suggestions for safe limits of _____, providing an estimation for systemic exposure. In addition, for small molecule weight compounds, we expect a human equivalent dose or intake be calculated based on the body surface area. Your calculation of the maximum allowable daily intake (ADI) used a mg/kg approach, resulting in an acceptable _____ . An intake based on the body surface area will result in an ADI of _____ . Please tighten your acceptance criterion for: _____ and provide adequate justification for the adjusted proposed level.
- 2) Please provide the actual levels of: _____ that have been administered to patients in clinical trials. This information should include the total amount of: _____ administered per dose of the drug product.

b(4)

b(4)

Please confirm receipt of this information request.
Thank you,
Lisa

From: Denise Hayes
To: Skarupa, Lisa;
cc: Jean Nichols; Joan Shankle;
Subject: RE: NDA 22393 information request
Date: Monday, June 22, 2009 10:57:49 AM

Hi Lisa:

The Gloucester team received this request and we are initiating the work to prepare a response.

Best regards,
Denise

From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Friday, June 19, 2009 1:28 PM
To: Denise Hayes
Subject: NDA 22393 information request

Good afternoon Denise,
Please see attached information request.
<<NDA 22393 Information Request June 19 2009.pdf>>
Please let me know when you have received it.
Lisa

We are interested in the following sensitivity analyses but having difficulty to accomplish them, because the inconsistency of subject IDs, concomitant medication classifications, and treatment onset and ending dates in your raw datasets. Would you please provide us the following analysis results, derived datasets for these analyses, listing of involved raw datasets, and programs:

1. Overall response rate and CR in TP of each study both INV and IRC assessments, by subgroup of
 - a. concomitant therapies (topical or systemic antibiotics, radiation and surgery for local disease)
 - b. prior therapies- number of the systemic therapies, prior Ontak, prior Targretin or both.
 - c. disease stages
2. Estimations of the duration of ORR for above subgroups.

Also, please provide the following:

1. Please include unique patient identifier (USUBJID, same variable as derived datasets) in all datasets of both GPI-04-0001 and NCI 1312 studies.
2. Please clarify whether there were any concomitant local radiation therapies for any subjects of study GPI-04-0001.
3. Please define column "workfl" in the dataset ACONME_1 and explain how it was derived.

For both GPI-04-0001 and NCI 1312 studies:

The derived dataset with unique record per patient may (not limited to) include below variables:

1. Trial number, unique patient identifier (USUBJID, the same as ISE submission), NCI pt #, the trial pt # , TP (yes vs. No), EP (Yes vs. No),
2. IRRC CR (Yes vs. No), duration of IRRC CR, IRRC CR date of response, IRRC CRp (Yes vs. No), duration of IRRC CRp, IRRC CRp date of response, IRRC ORR (IRRC CR or CRp, yes vs. no), duration of IRRC ORR, IRRC ORR date of response,
3. Investigator CR (Yes vs. No), duration of investigator CR, investigator CR date of response, investigator CRp (Yes vs. No), duration of investigator CRp, investigator CRp date of response, investigator ORR (IRRC CR or CRp, yes vs. no), duration of investigator ORR, investigator ORR date of response,
4. Concomitant therapies (Yes vs. no), flag of topical therapies (Yes vs. no), flag of systemic antibiotics (yes vs. no), flag of radiation (yes vs. no), flag of surgery for local disease (yes vs. no), flag of prior therapies (yes vs. no), number of prior systemic therapies (yes vs. no), prior Ontak therapies (yes vs. no), first prior Ontak therapies date, last prior Ontak therapies date, prior Targretin therapies (yes vs. no), first prior Targretin therapies date, last prior Targretin therapies date, prior Ontak or Targretin therapies (yes vs no), disease stages.
5. Cycle and day of each tumor measurement below
6. Day on study of each tumor measurement below
7. Tumor measurements (lymph node, visceral) in a format that allows the longest diameters to be summed
8. Tumor measurements (Sezary cells) yes/no/not assessable
9. Tumor measurements (skin): If data is available that distinguishes skin patches/plaques, tumors and areas of erythroderma and provides the longest diameter of each lesions, please put this in a format that allows us to sum these measurements. Otherwise, it is only necessary to include the variable SKCOMPAR.

For both GPI-04-0001 and NCI 1312 studies:

The derived dataset with multiple records per patient may (not limited to) include below variables:

- Trial number, unique patient identifier (USUBJID),
- systemic antibiotics drug names (one drug per row),
- first systemic treatment date, last systemic treatment date,
- flag of anti-bacteria (yes vs. no), flag of anti-fungi (yes vs. no), flag of antiviral (yes vs. no),
- topical therapies (one drug per row), first topical treatment date, last topical treatment date,
- radiation (each type in each row), radiation dates (1st, 2nd, 3rd, ... last),
- surgery for local disease name (each surgery in each row), procedure date,
- prior systemic antibiotics drug names (one drug per row),
- first prior systemic treatment date, last prior systemic treatment date

Please state when this dataset will be available. Please note that we may have additional requests.

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/s/

Lisa M Skarupa
6/22/2009 12:26:56 PM

From: Skarupa, Lisa
Sent: Friday, June 19, 2009 1:28 PM
To: 'Denise Hayes'
Subject: NDA 22393 information request

Good afternoon Denise,
Please see attached information request.



NDA 22393
Information Request .

Please let me know when you have received it.
Lisa

We are interested in the following sensitivity analyses but having difficulty to accomplish them, because the inconsistency of subject IDs, concomitant medication classifications, and treatment onset and ending dates in your raw datasets. Would you please provide us the following analysis results, derived datasets for these analyses, listing of involved raw datasets, and programs:

1. Overall response rate and CR in TP of each study both INV and IRC assessments, by subgroup of
 - a. concomitant therapies (topical or systemic antibiotics, radiation and surgery for local disease)
 - b. prior therapies- number of the systemic therapies, prior Ontak, prior Targretin or both.
 - c. disease stages
2. Estimations of the duration of ORR for above subgroups.

Also, please provide the following:

1. Please include unique patient identifier (USUBJID, same variable as derived datasets) in all datasets of both GPI-04-0001 and NCI 1312 studies.
2. Please clarify whether there were any concomitant local radiation therapies for any subjects of study GPI-04-0001.
3. Please define column "workfl" in the dataset ACONME_1 and explain how it was derived.

For both GPI-04-0001 and NCI 1312 studies:

The derived dataset with unique record per patient may (not limited to) include below variables:

1. Trial number, unique patient identifier (USUBJID, the same as ISE submission), NCI pt #, the trial pt #, TP (yes vs. No), EP (Yes vs. No),
2. IRRC CR (Yes vs. No), duration of IRRC CR, IRRC CR date of response, IRRC CRp (Yes vs. No), duration of IRRC CRp, IRRC CRp date of response, IRRC ORR (IRRC CR or CRp, yes vs. no), duration of IRRC ORR, IRRC ORR date of response,
3. Investigator CR (Yes vs. No), duration of investigator CR, investigator CR date of response, investigator CRp (Yes vs. No), duration of investigator CRp, investigator CRp date of response, investigator ORR (IRRC CR or CRp, yes vs. no), duration of investigator ORR, investigator ORR date of response,
4. Concomitant therapies (Yes vs. no), flag of topical therapies (Yes vs. no), flag of systemic antibiotics (yes vs. no), flag of radiation (yes vs. no), flag of surgery for local disease (yes vs. no), flag of prior therapies (yes vs. no), number of prior systemic therapies (yes vs. no), prior Ontak therapies (yes vs. no), first prior Ontak therapies date, last prior Ontak therapies date, prior Targretin therapies (yes vs. no), first prior Targretin therapies date, last prior Targretin therapies date, prior Ontak or Targretin therapies (yes vs no), disease stages.
5. Cycle and day of each tumor measurement below
6. Day on study of each tumor measurement below

7. Tumor measurements (lymph node, visceral) in a format that allows the longest diameters to be summed
8. Tumor measurements (Sezary cells) yes/no/not assessable
9. Tumor measurements (skin): If data is available that distinguishes skin patches/plaques, tumors and areas of erythroderma and provides the longest diameter of each lesions, please put this in a format that allows us to sum these measurements. Otherwise, it is only necessary to include the variable SKCOMPAR.

For both GPI-04-0001 and NCI 1312 studies:

The derived dataset with multiple records per patient may (not limited to) include below variables:

Trial number, unique patient identifier (USUBJID),
systemic antibiotics drug names (one drug per row),
first systemic treatment date, last systemic treatment date,
flag of anti-bacteria (yes vs. no), flag of anti-fungi (yes vs. no), flag of antiviral (yes vs. no),
topical therapies (one drug per row), first topical treatment date, last topical treatment date,
radiation (each type in each row), radiation dates (1st, 2nd, 3rd, ... last),
surgery for local disease name (each surgery in each row), procedure date,
prior systemic antibiotics drug names (one drug per row),
first prior systemic treatment date, last prior systemic treatment date

Please state when this dataset will be available. Please note that we may have additional requests.

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Lisa M Skarupa
6/18/2009 10:07:35 AM

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Lisa M Skarupa
6/15/2009 12:13:11 PM

From: Skarupa, Lisa
Sent: Friday, June 05, 2009 11:44 AM
To: 'Denise Hayes'
Subject: Information request for NDA22393

Hello Denise,

Please see the following Information request:

The enrollment number based on the NDA 22393 clinical study report table 2-1 and 2-13 are summarized in the table below.

Study ID	GPI-04-0001	NCI 1312			
		All	Arm 1	Arm 3	Arm 5
Enrolled	96	?	?	?	?
Received > one dose study drug	96	71	27	15	29

1. Please clarify the enrollment number of study NCI 1312, total and each arm.
2. Please clarify whether all enrolled patients had received at least one dose of study drug.

Please confirm receipt.

Thank you,
Lisa

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/s/

Lisa M Skarupa
6/5/2009 12:58:35 PM

From: Denise Hayes [mailto:denise.hayes@gloucesterpharma.com]
Sent: Friday, June 05, 2009 11:55 AM
To: Skarupa, Lisa
Subject: RE: Information request for NDA22393

Hi Lisa:
I received this request for information and am passing it on to the Gloucester team.
Denise

From: Skarupa, Lisa
Sent: Friday, June 05, 2009 11:44 AM
To: 'Denise Hayes'
Subject: Information request for NDA22393

Hello Denise,

Please see the following Information request:

The enrollment number based on the NDA 22393 clinical study report table 2-1 and 2-13 are summarized in the table below.

Study ID	GPI-04-0001	NCI 1312			
		All	Arm 1	Arm 3	Arm 5
Enrolled	96	?	?	?	?
Received \geq one dose study drug	96	71	27	15	29

1. Please clarify the enrollment number of study NCI 1312, total and each arm.
2. Please clarify whether all enrolled patients had received at least one dose of study drug.

Plas confirm receipt.

Thank you,
Lisa

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/s/

Lisa M Skarupa
6/5/2009 12:58:35 PM



NDA 22-393

**PROPRIETARY NAME REQUEST
- CONDITIONALLY ACCEPTABLE**

Gloucester Pharmaceuticals
ATTENTION: Jean Nichols, Ph.D., President & Chief Operating Officer
One Broadway, 14th Floor
Cambridge, Massachusetts 02142

Dear Dr. Nichols:

Please refer to your New Drug Application (NDA) dated January 12, 2009, received January 12, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for romidepsin powder for injection, 10 mg.

We also refer to your February 4, 2009, correspondence, received February 4, 2009, requesting a review of your proposed proprietary name, Istodax. We have completed our review of the proposed proprietary name, Istodax and have concluded that it is acceptable. Istodax 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 you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Sandra Griffith, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager.

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/

Robert Justice
4/30/2009 06:03:27 PM