

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

REQUEST FOR CONSULTATION

TO (Division/Office) HFD-110/Denise Hinton/Devi Kozeli (IRT)			FROM: HFD-150/Lisa Skarupa, RPM				
DATE April 10, 2009	IND NO.	NDA NO. 22393	TYPE OF DOCUMENT New NDA - NME	DATE OF DOCUMENT Jan 12, 2009			
NAME OF DRUG: romidepsin (FK228, Depsipeptide, FR901228, NSC630176) intravenous		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE as priorities permit			
NAME OF SPONSOR: Gloucester Pharmaceuticals, Inc., Cambridge, MA							
REASON FOR REQUEST							
I. GENERAL							
<table style="width: 100%; border: none;"> <tr> <td style="width: 33%; vertical-align: top;"> NEW PROTOCOL PROGRESS REPORT NEW CORRESPONDENCE DRUG ADVERTISING ADVERSE REACTION REPORT MANUFACTURING CHANGE/ADDITION MEETING PLANNED BY </td> <td style="width: 33%; vertical-align: top;"> PRE-NDA MEETING END OF PHASE II MEETING RESUBMISSION SAFETY/EFFICACY PAPER NDA CONTROL SUPPLEMENT </td> <td style="width: 33%; vertical-align: top;"> RESPONSE TO DEFICIENCY LETTER (fax) FINAL PRINTED LABELING LABELING REVISION ORIGINAL NEW CORRESPONDENCE FORMULATIVE REVIEW OTHER (SPECIFY BELOW)- Original NDA with IRT </td> </tr> </table>					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)- Original NDA with IRT
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II. BIOMETRICS							
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TYPE A OR B NDA REVIEW END OF PHASE II MEETING CONTROLLED STUDIES PROTOCOL REVIEW OTHER			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							
9 CLINICAL			9 PRECLINICAL				
COMMENTS/SPECIAL INSTRUCTIONS: QTc protocol and IRT consult is requested for this NDA submission. Our Mid-Cycle will be June 12, 2009. It was submitted via CDER eDR, the link is: \\CDSESUB1\EVSPROD\NDA022393\0000 . Please let me know if you have any questions. The Medical Officer is Dr. Qin Ryan.							
SIGNATURE OF REQUESTER Lisa Skarupa			METHOD OF DELIVERY (Check one) <input type="checkbox"/> FAX <input checked="" type="checkbox"/> Electronic				
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER				

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/s/

Lisa M Skarupa
4/17/2009 03:14:29 PM

From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Tuesday, April 14, 2009 3:48 PM
To: Denise Hayes
Subject: RE: NDA 22-393 - Follow-up to filing letter requests

Denise,

I am not sure if you had seen this request before, it seems that the SAS transport files and SAS programs emails were sent at the same time. Can you confirm that you received this request via emails (see below).

Please submit all SAS programs to product the statistical results in section 11 of study NCI 1312 and GPI-04-0001. Please also provide a documented file to indicate which program is for which result.

When SAS files were found to be corrupt, I thought that they were all going to be replaced. Nevertheless, please let me know if this can be sent soon.

Lisa



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-393

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 also refer to your submissions dated February 11 and 18, 2009.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Standard. Therefore, the user fee goal date is November 12, 2009.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests between October 5 and 9, 2009.

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

1. The Pharmacokinetics dataset for study AN10018a is not in SAS transport file (*.xpt).

2. The submitted draft labeling is not in compliance with Physician's Labeling Rule.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

1. Resubmit pharmacokinetics dataset for study AN10018a in SAS transport file (*.xpt).
2. Inclusion of "Dosage form" and "Route of administration" in Highlights of Prescribing Information.
3. Inclusion of "Use in Specific Populations" in Highlights of Prescribing Information.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

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

REQUIRED PEDIATRIC ASSESSMENTS

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

Because ISTODAX (romidepsin) for infusion has orphan drug designation for this indication, you are exempt from this requirement.

NDA 22-393

Page 3

If you have any questions, call Lisa Skarupa, Regulatory Project Manager, at (301) 796-2219.

Sincerely,

{See appended electronic signature page}

Robert Justice, M.D.
Division Director
Division of Drug Oncology Products
Office of Oncology Drug Products

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/s/

Frank Cross
3/23/2009 04:36:14 PM

Robert Justice
3/23/2009 05:21:29 PM

DSI CONSULT: Request for Clinical Inspections

Date: February 23, 2009

To: Constance Lewin, M.D., M.P.H., Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief (Acting), GCP2
Robert Young, M.D., Medical Officer
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Qin Ryan, M.D., Medical Officer, DDOP
Virginia E. Maher, M.D., Medical Team Leader, DDOP
Robert Justice, M.D., Division Director, DDOP

From: Lisa Skarupa, Regulatory Project Manager, HFD-150

Subject: Request for Clinical Site Inspections

I. General Information

Application#: NDA-22-393

Applicant/ Applicant contact information (to include phone/email):

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

Drug Proprietary Name: ISTODAX (romidepsin)

NME or Original BLA (Yes/No): NME

Review Priority (Standard or Priority): Priority

Study Population includes < 17 years of age (Yes/No): No

Is this for Pediatric Exclusivity (Yes/No): No, drug received orphan designation.

Proposed New Indication(s): Treatment of cutaneous T-cell lymphoma, including relief of pruritus
in patients who have received at least one prior systemic therapy.

PDUFA: July 12 2009

Action Goal Date: June 20, 2009

Inspection Summary Goal Date: May 26, 2009

DSI Consult

version: 5/08/2008

II. Protocol/Site Identification

GPI-04-0001 “A Single Agent Phase II Study of Depsipeptide (FK228) in the Treatment of Cutaneous T-cell Lymphoma”

NCI-1312 “Phase II Trial of Depsipeptide in Patients with Cutaneous T-cell Lymphoma and Relapsed Peripheral T-cell Lymphoma”

Two single arm studies, GPI-04-0001 and NCI1312, have been submitted to support the approval of Romidepsin for second line treatment of patients with CTCL. Based on the enrollment, response rate, serious adverse events, protocol violations, and location, the sites that are thought to be essential for approval, have been identified for inspection. These sites are listed in order of priority in the table on next page.

III. Site Selection/Rationale

The efficacy and safety results of two single arm studies, GPI-04-0001 and NCI1312, have been submitted to support the approval of Romidepsin for the second line treatment of patients with CTCL. Based on the enrollment, response rate, number of serious adverse events, major violations, and location, these sites which thought to be essential for approval have been identified for inspection. Site #2 in protocol GPI-04-0001 has the highest accrual. Other sites in the U.S. (other than site #48) have accrued only 2-3 patients. Therefore, inspection of site #2 under GPI-04-0001 is considered essential. The NCI Extramural Study Center in protocol NCI-1312 accrued the second highest number of patients. Other study sites accrued much smaller numbers of patients with this rare disease. However, no financial conflict reported on any sites or studies.

Rationale for DSI Audits

The clinical team would like to ensure the adequacy of the clinical data report, collection and handling at each study site interested. Specifically, whether there is any discrepancy between the CRF and primary source documents of each subject in the following areas.

- AEs, SAEs, deaths, or discontinuations
- Efficacy evaluation, tumor measurement documentation, photographic documentation, documentations of patient’s skin appearance and related symptoms.
- Any protocol violations of enrollment, conduct, or discontinuation

Site # (Name, Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Number of CR or PR	Number of deaths	Number of SAEs	Number of major protocol violations	Indication
SITE #2 Dr. Sean Whittaker St John's Institute of Dermatology, St. Thomas' Hospital Lambeth Palace Road London SE1 7EH, UK	GPI-04-0001	12	3	1	3	3	CTCL
SITE #48 Dr. Adam Lerner Boston Medical Center, Center for Cancer and Blood Disorders 732 Harrison Avenue Boston, MA 02118, USA	GPI-04-0001	6	4	0	1	1	CTCL
SITE: NCI Intramural Study Center Susan Bates, MD (Principal and Coordinating Investigator) Richard Piekartz, MD, PhD (Protocol Chairman) National Cancer Institute 9000 Rockville Pike Bethesda, MD 20892	NCI-1312	39	11	2	23	5	CTCL, RPTCL
SITE: NCI Extramural Study Center Prince, Miles, MBBS (Hons), MD, MRACMA, FRACP Peter MacCullum Cancer Centre Centre for Blood Cell Therapies, St. Andrew's Place East Melbourne, Victoria, Australia	NCI-1312	15	7	1	8	0	CTCL, RPTCL

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): See section III.

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

See section III.

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact Lisa Skarupa, RPM 301-796-2219 or Qin Ryan, M.D., at 301-796-2330.

Concurrence: (as needed)

_____ Virginia E. Maher, M.D., Medical Team Leader
 _____ Qin Ryan, M.D., Medical Reviewer
 _____ Robert Justice, M.D., Division Director (for foreign inspection requests or requests for 5 or more sites only)

*****Things to consider in decision to submit request for DSI Audit**

- Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?
- Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?
- Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?
- Are there concerns that the data may be fraudulent or inconsistent?
 - Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action
 - Expected commonly reported AEs are not reported in the NDA
- Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?
- Is this a new molecular entity or original biological product?
- Is the data gathered solely from foreign sites?
- Were the NDA studies conducted under an IND?

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/s/

Qin Ryan
3/11/2009 04:56:30 PM

Virginia E Maher
3/11/2009 05:06:31 PM

Robert Justice
3/12/2009 06:15:06 PM
Review priority changed to standard.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22393

Applicant: Gloucester

Stamp Date: Jan 12, 2009

Drug Name: Romidepsin

NDA/BLA Type: Original

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			It appears to be acceptable.
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			It appears to be acceptable.
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	x			It appears to be acceptable.
5.	Are all documents submitted in English or are English translations provided when necessary?	x			It appears to be acceptable.
6.	Is the clinical section legible so that substantive review can begin?	x			It appears to be acceptable.
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			It appears to be acceptable.
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	x			It appears to be acceptable.
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			It appears to be acceptable.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			It appears to be acceptable.
11.	Has the applicant submitted a benefit-risk analysis for the product?			x	Not yet found in the submission
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	x			505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: Study Title: T-95-0022 Phase 1 study under IND 51,810 Sample Size: 33 Arms: one Location in submission: 5.3.3.2	x			It appears to be acceptable.
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: Study GPI-04-0001 Indication: Second line treatment for advanced CTCL	x			Single arm studies only

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2: Study NCI 1312 Indication: Second line treatment for advanced CTCL				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			Single arm studies only, will have ODAC discussion
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			CR + Cru rate was FDA recommend primary endpoints. The study primary endpoint was ORR. The symptom improvement endpoint was in question.
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	Not found yet
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			It appears to be acceptable.
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	x			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			It appears to be acceptable.
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			x	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	x			It appears to be acceptable.
24.	Has the applicant adequately evaluated the safety issues that	x			It appears to be

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	are known to occur with the drugs in the class to which the new drug belongs?				acceptabl, but I have not had time to looked into the details.
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			It appears to be acceptable.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			x	Orphan status
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	Not found yet
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	Not found yet
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			It appears to be acceptable.
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			It appears to be acceptable.
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			It appears to be acceptable.
34.	Are all datasets to support the critical safety analyses available and complete?	x			It appears to be acceptable.
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			It appears to be acceptable.
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			It appears to be acceptable.
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			It appears to be acceptable.
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			It appears to be acceptable.
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			It appears to be acceptable.

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _____

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None at the moment.

Qin Ryan, MD, PhD	Feb 25, 2009
Reviewing Medical Officer	Date
Virginia E. Maher, MD	Feb 25, 2009
Clinical Team Leader	Date

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/s/

Virginia E Maher
3/11/2009 11:40:49 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-393

**PROPRIETARY NAME REQUEST
ADVICE**

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 Lyophilized Powder, 10 mg per vial.

We also acknowledge receipt of your February 4, 2009, correspondence, received February 4, 2009, requesting a review of your proposed proprietary name, ISTODAX. We note that you have also included an alternate proprietary name, _____ in your submission. We will not initiate review of this alternate name as part of this review cycle. If the proposed proprietary name, ISTODAX, is denied, you will be notified and you must submit a new complete request for review of the alternate name.

b(4)

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

Sincerely,

Frank Cross, Jr.
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Frank Cross

3/9/2009 12:05:14 PM

REQUEST FOR CONSULTATION

TO (Division/Office) HFD-805 Jim McVey, Ph.D., Team Leader David Hussong, Ph.D., Director Scientist		FROM: HFD-150/ Lisa Skarupa, RPM, 301-796-2219		
DATE February 24, 2009	IND NO.	NDA NO. 22-393	TYPE OF DOCUMENT New NDA – NME	DATE OF DOCUMENT January 12, 2009
NAME OF DRUG: romidepsin (FK228, Depsipeptide, FR901228, NSC630176) intravenous		PRIORITY CONSIDERATION Priority	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE June 1, 2009

NAME OF SPONSOR: Gloucester Pharmaceuticals, Inc., Cambridge, MA

REASON FOR REQUEST

I. GENERAL

NEW PROTOCOL PROGRESS REPORT NEW CORRESPONDENCE DRUG ADVERTISING ADVERSE REACTION REPORT MANUFACTURING CHANGE/ADDITION MEETING PLANNED BY DDOP	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
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II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
TYPE A OR B NDA REVIEW END OF PHASE II MEETING CONTROLLED STUDIES PROTOCOL REVIEW OTHER	CHEMISTRY REVIEW PHARMACOLOGY BIOPHARMACEUTICS OTHER

III. BIOPHARMACEUTICS

DISSOLUTION BIOAVAILABILITY/PK STUDIES PHASE IV STUDIES	DEFICIENCY LETTER RESPONSE PROTOCOL-BIOPHARMACEUTICS IN-VIVO WAIVER REQUEST
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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
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V. SCIENTIFIC INVESTIGATIONS

CLINICAL	PRECLINICAL
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COMMENTS/SPECIAL INSTRUCTIONS: This is a new NDA submitted for priority review. Please see link to eDR.

\\CDSESUB1\EVSPROD\NDA022393\0000. The medical officer – Dr. Qin Ryan.

SIGNATURE OF REQUESTER Lisa Skarupa	METHOD OF DELIVERY (Check one) <input type="checkbox"/> FAX <input checked="" type="checkbox"/> ELECTRONIC
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Lisa M Skarupa
2/24/2009 01:03:13 PM

REQUEST FOR CONSULTATION

TO (Division/Office) HFD-410 OSE, Sandra Griffith
Labeling to DMEPA with PPI and carton container

FROM: HFD-150/Lisa Skarupa

DATE January 12, 2009	IND NO.	NDA NO. 22-393	TYPE OF DOCUMENT NEW NDA	DATE OF DOCUMENT January 12, 2009
NAME OF DRUG: romidepsin (FK228, Depsipeptide, FR901228, NSC630176) intravenous		PRIORITY CONSIDERATION Priority	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE June 1, 2009

NAME OF SPONSOR: Gloucester Pharmaceuticals, Inc., Cambridge, MA

REASON FOR REQUEST

I. GENERAL

NEW PROTOCOL PROGRESS REPORT NEW CORRESPONDENCE DRUG ADVERTISING ADVERSE REACTION REPORT MANUFACTURING CHANGE/ADDITION MEETING PLANNED BY	PRE-sNDA 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
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II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
TYPE A OR B NDA REVIEW END OF PHASE II MEETING CONTROLLED STUDIES PROTOCOL REVIEW OTHER	CHEMISTRY REVIEW PHARMACOLOGY BIOPHARMACEUTICS OTHER

III. BIOPHARMACEUTICS

DISSOLUTION BIOAVAILABILITY/PK STUDIES PHASE IV STUDIES	DEFICIENCY LETTER RESPONSE PROTOCOL-BIOPHARMACEUTICS IN-VIVO WAIVER REQUEST
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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
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V. SCIENTIFIC INVESTIGATIONS

9 CLINICAL	9 PRECLINICAL
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COMMENTS/SPECIAL INSTRUCTIONS: This is a new NDA submitted for priority review. Please see link to eDR.
 \\CDSESUB1\EVSPROD\NDA022393\0000. Carton and container submitted 18Feb09. **The medical officer – Dr. Qin Ryan.**

SIGNATURE OF REQUESTER Lisa Skarupa	METHOD OF DELIVERY (Check one) <input type="checkbox"/> FAX <input checked="" type="checkbox"/> Electronic
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Lisa M Skarupa
2/24/2009 01:31:31 PM



NDA 22-393

NDA ACKNOWLEDGMENT

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

Dear Dr. Jean Nichols:

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

Name of Drug Product: ISTODAX (romidepsin), lyophilized powder, intravenous

Date of Application: January 12, 2009

Date of Receipt: January 12, 2009

Our Reference Number: NDA 22-393

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 13, 2009 in accordance with 21 CFR 314.101(a).

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

Please note that you are responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) (42 USC §§ 282(i) and (j)), which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) (42 USC § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been

met. Where available, the certification must include the appropriate National Clinical Trial (NCT) control numbers. 42 USC 282(j)(5)(B). You did not include such certification when you submitted this application. You may use Form FDA 3674, *Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank*, to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trials referenced in this application. Additional information regarding the certification form is available at: http://internet-dev.fda.gov/cder/regulatory/FDAAA_certification.htm. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information on registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

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

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

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

If you have any questions, call Lisa Skarupa, Regulatory Project Manager, at (301) 796-2219.

Sincerely,

{See appended electronic signature page}

Lisa Skarupa, RN, MSN, AOCN
Regulatory Project Manager
Division of Oncologic Drug Products
Center for Drug Evaluation and Research

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/s/

Lisa M Skarupa
2/19/2009 11:19:00 AM

FDA ATTENDEES: Robert Justice, M.D., Acting Division Dir., DODP
Ramzi Dagher, M.D., Medical Team Leader, DODP
Rajeshwari Sridhara, Ph.D., Statistics Team Leader, DBI
W. David McGuinn, Ph.D., Pharmacologist, DODP
Sophia Abraham, Ph.D., Clin. Pharm./Bioph. Reviewer, DODP
Atik Rahman, Ph.D., Clin.Pharm./Bioph. Team Leader, DODP
Nallaperumal Chidambaram, Ph.D., Chemistry Team Leader, DNDC I
Haripada Sarker, Ph.D., Chemistry Reviewer, DNDC I
Nicholette Hemingway, Project Manager, DODP

SPONSOR ATTENDEES: William McCulloch, M.D., Chief Medical Officer,
Gloucester
John Wright, M.D., Ph.D., NCI Program Head for
depsipeptide
Mitchell Keegan, Ph.D., Senior Dir., Drug Dev., Gloucester
Nick Vrolijk, Ph.D., VP of Manufacturing Operations,
Gloucester
_____ Regulatory Consultant, Gloucester
_____ M.S., Senior Biostatistician, _____
_____, M.S., M.A., RAC, Senior Dir.,
Regulatory Operations, _____
_____ M.S., RAC, Project Manager,
Regulatory Operations, _____

b(4)

PURPOSE OF MEETING: To discuss sponsor's preliminary data presentation scenarios for clinical data obtained on studies conducted by NCI with depsipeptide in preparation for NDA submission in 2006. Sponsor wants to discuss CTCL, PTCL pivotal trial design, plus comparability study for new supplier of API. This meeting is in response to meeting requests dated May 4, 2005 (SN-029) and May 11, 2005 (SN-030).

IND 63,573 Sponsor Questions and FDA Responses(SN-034, Meeting Package dated June 10, 2005):

1. [Clinical/statistical question] Sections 9.2.1 and 9.2.2 describe Gloucester's presentation plan and data integration summary for reports, data, and case report forms (CRFs) from clinical studies conducted by Gloucester, Fujisawa, and the NCI in the NDA. Does the FDA agree with following presentation strategies?
 - a) Preparation of full clinical study reports (CSRs) that include both efficacy and safety data for studies GPI-04-0001 (CTCL), FJ-228-0001 (renal cell carcinoma), FJ-228-0002 (prostate cancer), and NCI 1312 (CTCL patients only); and preparation of study synopses¹, limited to available safety data as described in Table 4, for all other studies.
 - b) Inclusion of data from studies GPI-04-0001 (CTCL) and NCI 1312 (CTCL patients only), in the integrated summary of efficacy (ISE) with additional supportive CTCL patient data from other studies as available.
 - c) Databases from studies GPI-04-0001, FJ-228-0001, and FJ-228-0002 will be submitted in the electronic submission, and databases for the remaining studies and associated documentation will be submitted separately from the electronic component. The database from the NCI 1312 study will be included in the electronic submission if an appropriate database is available.
 - d) Inclusion of CRFs (where available) only for patients with disease progression, serious adverse events, and withdrawals due to adverse events; and for patient deaths. Additionally, CRFs and photographs (where available) will be included for CTCL responders. The availability of complete CRFs may be limited for studies conducted by the NCI.

FDA – In general, your strategy appears appropriate; however, we encourage you to submit the NCI 1312 database electronically. We recommend that you review your study results for CTCL with us in a pre-NDA meeting prior to submitting the NDA.

2. [Clinical/statistical question] Sections 9.1 through 9.1.3.2 describe clinical studies conducted by Gloucester, Fujisawa, and the NCI and the associated data management/quality assurance procedures. Data management/quality assurance procedures for the Gloucester- and Fujisawa-sponsored studies are consistent with pharmaceutical industry and GCP standards. Data management/quality assurance procedures for NCI-sponsored studies, including NCI study 1312, differ from the
-

pharmaceutical industry standard. After verifying the availability, completeness, and quality of the database for the NCI study 1312, it may be necessary to update this database retrospectively, where possible, using available source data at the study sites (see Section 0). Based on the presentation plan and data integration strategy described in Question 1 and in Sections 9.2.1 through 9.2.2, are these data management/quality assurance procedures acceptable to the FDA to ensure quality of the data to be included in the NDA?

FDA - This will depend on the amount and nature of missing data.

3. [Clinical/statistical question] Section 9.2.2 identifies the safety and efficacy data parameters available for all clinical studies conducted by Gloucester, Fujisawa, and the NCI. Does the FDA agree that data presented according to this availability meet FDA expectations for integrated safety and efficacy databases?

FDA - Please clarify why skin lesion measurements will not be available from GPI-04-0001 as indicated in Table 5.

Discussion- Sponsor has clarified that information on skin involvement will be available with respect to total body involvement as previously reviewed in the SPA. Agency expects the efficacy results to be presented individually for the NCI and GPI studies. If the sponsor wishes to present a pooled efficacy analysis, this would be considered exploratory.

4. [Clinical/statistical question] Upon enrollment of 64 evaluable patients in study GPI-04-0001, and based on positive efficacy results, Gloucester intends to submit these data along with data from CTCL patients in the NCI 1312 study that are available at that time (evaluable patient total to meet or exceed 100). Is this strategy acceptable to the FDA?

FDA - This will depend on the study results. We strongly suggest that you review a summary of the efficacy and safety results with us in a pre-NDA meeting prior to submission.

5. [Clinical/statistical question] Some patients who show positive responses may be treated for an extended period of time on studies GPI-04-0001 and NCI 1312. Consequently, these studies would not be "complete" at the time of NDA submission. Full CSRs will be prepared using the data available at that time. Is this strategy acceptable to the FDA?

FDA - Yes.

6. [Pharmacology/toxicology] Gloucester considers that the FK228 safety and pharmacology program as described in Section 11 and summarized in Table 13, has met requirements of international conference on harmonisation (ICH) Guidelines M3(M) (Maintenance of the ICH Guidelines on Non-clinical Safety Studies for Conduct of Human Clinical Trials for Pharmaceuticals) and ICH S7A

(Safety Pharmacology Studies for Human Pharmaceuticals), and specific ICH guidelines referenced therein. Does the FDA agree with the following?

- a. No additional toxicity studies (repeat dose, reproduction, genotoxicity, carcinogenicity) will be required to support the NDA filing.

FDA - The battery of toxicology studies you have done does not include an assessment of long term exposure to Depsipeptide at the clinical schedule over repeated courses. Please provide a toxicology study wherein Depsipeptide is given to rats on days 1, 8, and 15 every 28 days for at least six courses. The highest dose should cause clinically observable toxicity. Additionally, your plan includes only one study of reproductive toxicity in rats (segment II). If this study fails to demonstrate reproductive toxicity you should plan to conduct a second study in rabbits.

Discussion- Sponsor will initiate the chronic toxicology study, however, this study may not be completed at time of NDA submission. This study will be underway at the time of the NDA submission. The need for a second reproductive toxicity study depends on the results of the first toxicity study. If required, this study will be underway at the time of the NDA submission. The sponsor will consult with the division for the need of a study in the second species after completion of the first study. This discussion will be expected by December of 2005.

- b. No additional nonclinical studies are required to address general and specific cardiac safety concerns raised during clinical development.

FDA - Your assessment of cardiac toxicity appears adequate at this time.

- c. The nonclinical studies conducted to date, combined with the planned clinical organ dysfunction (hepatic and renal) studies will sufficiently characterize FK228 and its metabolites for this indication without conducting further nonclinical or clinical ADME investigations.

FDA -Your non-clinical assessment of metabolism and pharmacokinetics appears adequate at this time. Please submit your proposed protocols for renal and hepatic impairment studies.

- d. Based on current understanding of FK228 metabolism (cytochrome p450 [CYP] 3A4), describing potential drug interactions in the product label will be adequate, and no additional studies are required to investigate possible specific drug interactions.

FDA - Your non-clinical assessment of cytochrome P450 interactions appears adequate at this time.

However, you have proposed foregoing *in vivo* inhibition and induction studies for CYP 3A4, and labeling against the use/or warning about the effect of strong inhibitors and inducers. These patients are susceptible to fungal infections, and without a study we would not know how to deal with either strong or moderate inhibitors of CYP 3A4. Therefore, we recommend that you conduct *in vivo* interaction studies with ketoconazole and rifampin, or other strong or moderate CYP 3A4 inhibitors and inducers. If the sponsor is unable to conduct *in vivo* interaction studies prior to NDA submission, the product labelling would include appropriate dosing information.

7. [Chemistry] Section 10 describes the proposed analytical comparability plan that will be implemented to demonstrate product comparability after transfer of the FK228 drug substance manufacturing process to a contract manufacturer. Please confirm that this plan is acceptable.

FDA – Your proposed plan appears to be acceptable. However, adequacy of your data will be evaluated at the time of submission.

PTCL

8. [Clinical/statistical question] Gloucester intends to conduct a PTCL trial. A formal sample size has not yet been determined, but the preliminary, estimated sample size is expected to be between 70 and 80 evaluable patients (assuming the hypothesized response rates specified in Section 10.3). These data will be supported by data from studies conducted by the National Cancer Institute (NCI) on approximately 30 PTCL patients and approximately 300 patients with other tumor types. Assuming that efficacy and patient benefit are demonstrated, does the FDA agree that approval could be obtained using this combination of efficacy data (approximately 100 evaluable patients)?

FDA - Please clarify what is meant by clinical benefit in this case. Given the heterogeneity of the patient population and the variability of organ, marrow and lymph node involvement, it will be necessary to specify your primary efficacy endpoint as clearly as possible. In your proposal, you refer to RECIST criteria and “other appropriate assessments.” The primary efficacy endpoint will have to be more specifically defined. If you intend to utilize a composite endpoint, this should be clearly outlined including a plan for analyzing such data and the contribution of each component to the overall assessment of response. We strongly recommend that you submit a proposed protocol for SPA so that we can comment on all aspects of trial design including primary endpoint and sample size.

9. [Clinical/statistical question] Considering the rarity of this disease and the lack of consensus on what represents “standard” therapy for PTCL, it is unlikely that any

randomized trial could be successfully conducted so Gloucester proposes to initiate a single-arm study to further investigate the NCI results (currently 25% objective response rate [ORR] with response duration of 8-19 months). As long as clear antitumor efficacy, in conjunction with evidence of patient benefit can be demonstrated, does the FDA agree that a comparative study is not necessary?

FDA - As mentioned above, this will depend on the nature of your planned primary efficacy endpoint and the outcome of the study. Please note that time-to-progression and survival cannot be evaluated for registration purposes in a single arm study.

10. [Clinical/statistical question] Assuming agreement on Question 2, Gloucester proposes to use ORR as the primary endpoint with duration of response and time to objective disease progression (TTP) included among secondary endpoints. Is this acceptable to the FDA?

FDA - See above

11. [Pharmacology/toxicology/clinical question] Gloucester intends to submit an NDA for the CTCL indication approximately 1 year before submitting the sNDA for _____ Based on approval of the CTCL application, does the FDA have any issues at this time for consideration/areas of concern regarding filing a supplemental application for _____ ?

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FDA - Not at this time.

Nicholette Hemingway
Project Manager

Concurrence Chair: _____
Ramzi Dagher, M.D.
Clinical Team Leader

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/s/

Ramzi Dagher
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FDA ATTENDEES: Richard Pazdur, M.D., Dir., DODP
Ramzi Dagher, M.D., Medical Team Leader, DODP
Qin Ryan, M.D., Medical Officer, DODP
W. David McGuinn, Ph.D., Pharmacologist, DODP
Sophia Abraham, Ph.D., Acting Clin. Pharm./Bioph. Team Leader, DODP
Gene Williams, Ph.D., Clin. Pharm./Bioph. Reviewer, DODP
Nicholette Hemingway, Project Manager, DODP

SPONSOR ATTENDEES: Jay Mohr, Chief Executive Officer, Gloucester Pharmaceuticals
William McCulloch, M.D., Chief Medical Officer, Gloucester
Pharmaceuticals
John Wright, M.D., NCI Program Head for depsipeptide
Richard Piekarz, M.D., NCI Investigator on protocol #1312
Tom Davis, M.D., NCI Lymphoma Specialist

1. Does the Agency consider that approval could be obtained using the NCI generated Phase II data in CTCL (on approximately 50 patients) with the support of data on a further 30 patients from a confirmatory trial sponsored by Gloucester Pharmaceuticals?

FDA Response: The sample size needs to be larger. In addition, three review issues are of concern:

- a) the mixed nature of the patient population,
- b) the concomitant local radiation therapy used in responders
- c) the duration of the response.

Discussion- 1a. Sponsor responded that 100 patients would be in the study, and FDA stated that sponsor needed to have a sufficient sample size to demonstrate clinical benefit. 1b. Discussion ensued concerning PR and CR definition and counts of evaluable lesions in responders. The sponsor clarified that the patients with resolution of all lesions but having some lesions treated by radiotherapy will not qualify for CR but PR. FDA also emphasized that duration of response would be an important factor in the efficacy review.

2. In view of the rarity of this disease, Gloucester proposes to initiate a single arm study to confirm the NCI results. Does the agency share our view that a comparative study may not be necessary to obtain approval so long as clear antitumor efficacy in conjunction with evidence of patient benefit can be demonstrated?

FDA Response: If the single arm approach is selected, the patient population would need to be carefully defined. This assumes the patients have sufficient extent and severity of disease that a tumor response could be assumed to represent clinical benefit, again emphasizing that the patient population must be well defined. In patients in whom standard therapy has failed, a single arm study might be sufficient. Well documented (photographs) objective tumor responses and response durations could be the primary endpoint.

Alternatively, if a less advanced population is evaluated, a randomized study would be required.

Discussion- The sponsor understands FDA's position.

3. Does the Agency consider that a general agreement can be reached before or during the end-of-phase II meeting on the design, endpoints and other parameters of the Sponsor's planned trial, based on the information provided in this package, without Gloucester requesting a Special Protocol Assessment per Guidance for Industry- Special Protocol Assessment, dated May 2002?

FDA Response: We strongly suggest that you submit a protocol for special protocol assessment.

4. Does the FK228 development program in CTCL qualify for fast-track designation?

FDA Response: Please submit a request for fast-track designation. A determination will be made at the time of submission.

5. Will the total number of patients exposed to FK228 (expected to reach over 300 by the time of the NDA submission) be sufficient as a safety database?

FDA Response: Yes.

6. In view of the fact that rigorous analysis has revealed that FK228 does not cause myocardial damage or affect left-ventricular function despite QTc and ST changes on ECG, does the Agency agree that it is reasonable to discontinue MUGA scans and serum troponin evaluations in future trials, unless clinically indicated?

FDA Response: After re-review of appendix 6, we agree with your proposal to discontinue MUGA scans and serum troponin evaluation in clinical trials, unless clinically indicated.

7. A commitment was made by Fujisawa to do rat, dog and human mass balance studies. To date a study has been conducted in rats (Report CRD 040009 submitted in Serial 021). Based on the similarity in metabolic pathways between all three species, and in view of the pharmacokinetic data obtained in the human Phase I studies and the data that will become available from Fujisawa's ongoing Phase II studies, Gloucester would propose to defer consideration of further mass balance studies until after NDA approval. Is this acceptable to the Agency?

FDA Response: The previously completed study in the rat will probably be sufficient to define mass balance non-clinically.

However, your plan to defer the mass balance studies in patients for FK228 until after approval of the NDA is not acceptable. How will you plan to make dosing recommendations in the label for the CTCL patients who have organ dysfunction (e.g., renal or hepatic)?

Discussion- Sponsor asked whether FDA needed the mass balance study done. At the meeting, the relationship between mass balance studies and studies in patients with impairment of eliminating organs was clarified. A mass balance study can result in a conclusion that either the kidney or the liver are not involved in drug elimination. This conclusion most frequently results in agreement that there is no need to study patients with impairment of the "not involved" organ. In the absence of a mass balance study, such a conclusion cannot be drawn. In such a case, FDA's usual expectation is that two studies will be completed prior to NDA filing: a study in subjects with renal impairment and a study in subjects with hepatic impairment. If such studies are not performed, there are implications for product labeling language.

Guidances on the topic of studies in organ-impaired subjects are present on the FDA Guidance site under the subheading "Clinical Pharmacology." The guidances are titled:

1. Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling, and
2. Pharmacokinetics in Patients with Impaired Renal Function.

John Wright commented that the Sponsor may want to consult with the NCI as they frequently conduct studies of investigational drugs in subjects with hepatic or renal impairment.

The FDA noted that if nearly all of a therapeutic dose is excreted as moieties for which reference standards and validated assays are available, it is not necessary to dose radiolabeled drug in order to accomplish a mass balance study.

8. Other non-clinical commitments to be performed before NDA submission were also discussed between Fujisawa and the FDA (see Table 8), including mutagenicity testing and toxicokinetic studies in animals. Since the mechanism of action of the drug and other features, including human PK have now become clearer, and sponsorship of the IND has changed, can the Sponsor and FDA review these commitments to ensure that there is mutual understanding of those that the FDA considers now necessary?

FDA Response: Please propose specific questions about the commitments Fujisawa made for the non-clinical development of FK228.

Discussion- FDA usually expects sponsor to perform the standard ICH battery of genotoxicity studies before the start of phase 3 clinical trials. Nevertheless, if the studies have not yet been initiated, sponsor can do them concurrently with the clinical trial– this requirement should not hold up the initiation of the trial. When the information from these studies is available, the sponsor should include it in the patient informed consent. Reproductive toxicity studies (segment II) are expected with the NDA package so the results may be included in the label.

Other Comments:

Sponsor will be submitting a fast-track designation request and a special protocol assessment (SPA) to the FDA for review.

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/s/

Qin Ryan
8/18/04 11:21:00 AM

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION		
NDA # 22-393 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: ISTODAX ® Established/Proper Name: romidepsin Dosage Form: Injection 10mg per single use vial		Applicant: Gloucester Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Lisa Skarupa		Division: Division of Oncology Drug Products
<p>NDAs: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p>
❖ User Fee Goal Date Action Goal Date (if different)		November 12, 2009 November 5, 2009
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		<input checked="" type="checkbox"/> None
❖ Promotional Materials (accelerated approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received {Not applicable} As per Applicant, Promotional Materials to be sent to DDMAC within 14 days after approval.

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

Application Characteristics ²	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC Comments: _____	
❖ Date reviewed by PeRC (<i>required for approvals only</i>) If PeRC review not necessary, explain: <u>Orphan Designation</u>	N/A, Orphan Designation
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)	<input type="checkbox"/> Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other FDA Press Release OODP Burst

² All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

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

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

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

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

Yes No

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

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

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

Yes No

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

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

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

Yes No

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

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

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

Yes No

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

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

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

<p>❖ Copy of this Action Package Checklist³</p>	<p>yes</p>
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Officer/Employee List (Not Applicable)

<p>❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p><input checked="" type="checkbox"/> Included</p>

Action Letters

<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Approval Letter with final labeling</p>
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Labeling

<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<p>January 12, 2009</p>
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
<p>❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)</p>	<p><input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> None</p>
<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	

³ Fill in blanks with dates of reviews, letters, etc.
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<ul style="list-style-type: none"> • Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent division proposal for (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	
❖ Proprietary Name <ul style="list-style-type: none"> • Review(s) (<i>indicate date(s)</i>) • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) 	November 4, 2009 April 16, 2009
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input type="checkbox"/> RPM <input type="checkbox"/> DMEPA August 6, 2009 <input type="checkbox"/> DRISK October 5, 2009 <input type="checkbox"/> DDMAC September 18, 2009 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	RPM Filing Review dated October 21, 2009
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant in on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters (except previous action letters), emails, faxes, telecons</i>)	Included
❖ Internal memoranda, telecons, etc.	Not applicable
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • PeRC (<i>indicate date of mtg; approvals only</i>) 	<input checked="" type="checkbox"/> Not applicable
<ul style="list-style-type: none"> • Pre-Approval Safety Conference (<i>indicate date of mtg; approvals only</i>) 	<input checked="" type="checkbox"/> Not applicable
<ul style="list-style-type: none"> • Regulatory Briefing (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
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<ul style="list-style-type: none"> • Other (e.g., EOP2a, CMC pilot programs) 	Not applicable
Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date(s) of Meeting(s) 	September 2, 2009
<ul style="list-style-type: none"> • 48-hour alert or minutes, if available (<i>do not include transcript</i>) 	Minutes included
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> November 5, 2009
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> November 2, 2009
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> October 16, 2009
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> Eight
Clinical Information	
❖ Clinical Reviews	
<ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	See Cross-Discipline TL Review Dated November 2, 2009
<ul style="list-style-type: none"> • Clinical review(s) (<i>indicate date for each review</i>) 	October 23, 2009
<ul style="list-style-type: none"> • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
❖ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)	See Clinical Review dated October 23, 2009
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	See Clinical Review dated October 23, 2009
❖ Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ Risk Management <ul style="list-style-type: none"> • REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>) • REMS Memo (<i>indicate date</i>) • Review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input checked="" type="checkbox"/> Review dated July 17, 2009
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> September 22, 2009
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> September 21, 2009
Clinical Pharmacology <input checked="" type="checkbox"/> None	

⁵ Filing reviews should be filed with the discipline reviews.
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❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> September 1, 2009
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input type="checkbox"/> October 20, 2009
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> October 20, 2009
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> October 19, 2009
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input type="checkbox"/> Maternal Health Team August 20, 2009
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> Included in P/T review
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> October 27, 2009
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Product quality review(s) (indicate date for each review)	<input type="checkbox"/> October 21, 2009
• ONDQA Biopharmaceutics review (indicate date for each review)	
• BLAs only: Facility information review(s) (indicate dates)	<input checked="" type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) (indicate date of each review)	<input type="checkbox"/> Review dated August 5, 2009
• BLAs: Sterility assurance, product quality microbiology (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	See CMC Review dated October 21, 2009
<input type="checkbox"/> Review & FONSI (indicate date of review)	
<input type="checkbox"/> Review & Environmental Impact Statement (indicate date of each review)	
❖ Facilities Review/Inspection	NONE
• NDAs: Facilities inspections (include EER printout) (date completed must be within 2 years of action date)	Date completed: June 22, 2009 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

<ul style="list-style-type: none">• BLAs:<ul style="list-style-type: none">○ TBP-EER ○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) <i>(date completed must be within 60 days prior to AP)</i>	<p>Date completed:</p> <p><input type="checkbox"/> Acceptable</p> <p><input type="checkbox"/> Withhold recommendation</p> <p>Date completed:</p> <p><input type="checkbox"/> Requested</p> <p><input type="checkbox"/> Accepted <input type="checkbox"/> Hold</p>
❖ NDAs: Methods Validation	<p><input type="checkbox"/> Completed</p> <p><input type="checkbox"/> Requested</p> <p><input type="checkbox"/> Not yet requested</p> <p><input checked="" type="checkbox"/> Not needed</p>