CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-393

CHEMISTRY REVIEW(S)

ONDQA Division Director's Memo
NDA 22-393, ISTODAX (romidepsin) for Injection
Date: 27-OCT-2009

Introduction

ISTODAX (romidepsin) for Injection (10 mg per single use vial) is indicated for the treatment of cutaneous T-cell lymphoma. The drug product is a lyophilized powder and it is co-packaged with a specified diluent. After addition of the specified diluent, the solution is to be further diluted with Normal Saline for intravenous infusion.

The recommended dose of romidepsin is 14 mg/m^2 administered intravenously over a 4-hour period on days 1, 8 and 15 of a 28-day cycle. Cycles should be repeated every 28 days provided that the patient continues to benefit from and tolerates the therapy.

The shelf life of the co-packaged drug product (active vial and diluent vial) is thirty six (36) months at controlled room temperature.

Adminstrative

The original submission of this 505(b)(1) new molecular entity NDA was received 12-JAN-2009 from Gloucester Pharmaceuticals Inc of Cambridge, MA. Three amendments which were received between 26-AUG-2009, and 09-OCT-2009 were also reviewed. This was a standard review time clock.

The application is supported by INDs 51,810 and 63,573. Consults for EES (22-JUN-2009), PharmTox (20-OCT-2009), and Microbiology (03-AUG-2009) were all Acceptable. More recently, ONDQA has reviewed container and carton labeling and found them to be acceptable.

There are no outstanding CMC deficiencies or agreements.

ONDQA recommends approval (AP).

Drug Substance (romidepsin)

The new molecular entity, romidepsin, is a white [redacted] powder. [redacted]

[redacted]

b(4)

Romidepsin is a bicyclic depsipeptide produced by [redacted] by [redacted] Romidepsin is stable at the storage condition of 25°C/60% RH. The proposed [redacted] retest period is acceptable based on the provided stability data.

Drug Product (ISTODAX)

The drug product is supplied as a kit containing two single-use vials (active and diluent). ISTODAX (romidepsin) for injection is a sterile lyophilized white powder and is supplied in a single-use vial containing 10 mg romidepsin formulated with 20 mg of Povidone, USP as a bulking agent.

The co-packaged diluent for ISTODAX is a sterile clear solution containing 80% (v/v) propylene glycol, USP and 20% (v/v) dehydrated alcohol, USP. It is supplied in a single-use vial containing a 2-mL deliverable volume.

The approved shelf-life of ISTODAX is 36 months when stored under controlled room temperature: 20°-25°C (68°-77°F); excursions permitted between 15°-30°C (59°-86°F).

Rik Lostritto, Ph.D., Director, ONDQA Division III

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

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/s/

RICHARD T LOSTRITTO
10/27/2009

NDA 22-393

ISTODAX® (romidepsin) for Injection

Gloucester Pharmaceuticals Inc

Ying Wang, PhD

Review Chemist

Office of New Drug Quality Assessment
Division of Pre-marketing Assessment and Manufacturing Science

For the Division of Oncology Products (HFD-150)

Table of Contents

CMC Review Data Sheet

1. NDA 22-393

2. REVIEW #: 1

3. REVIEW DATE: 12-OCT-2009

4. REVIEWER: Ying Wang, PhD

5. PREVIOUS DOCUMENTS:

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA	12-Jan-2009
Amendment (BC)	26-Aug-2009
Amendment (package insert Labeling)	09-Oct-2009
Amendment (container and carton labeling)	17-Sept-2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Gloucester Pharmaceuticals Inc
Address:	One Broadway 14th Floor Cambridge MA 02142 USA
Representative:	Jean Nichols, PhD, President and CEO
Telephone:	617-583-1314

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ISTODAX for injection
b) Non-Proprietary Name: romidepsin for injection
c) Code Name/# (ONDQA only):
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 1
- Submission Priority: S (Standard Review)

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Treatment of cutaneous T-cell lymphoma

CMC Review Data Sheet

11. DOSAGE FORM: Injection, Powder, Lyophilized, for Solution

12. STRENGTH/POTENCY: 10 mg/vial

13. ROUTE OF ADMINISTRATION: Intravenous Drip

14. Rx/OTC DISPENSED: __√__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__√__Not a SPOTS product

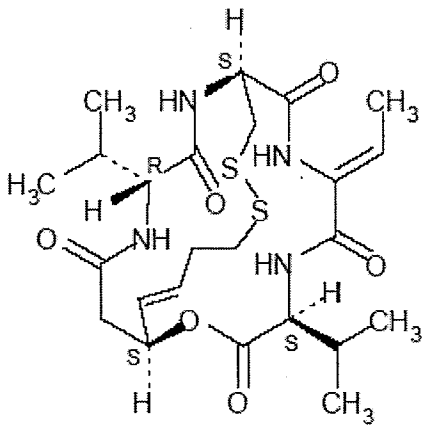
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

INN and USAN: romidepsin

IUPAC name:
(1S,4S,7Z,10S,16E,21R)-7-ethylidene-4,21-bis(1- methylethyl)-2-oxa-12,13-dithia-5,8,20,23- tetraazabicyclo[8.7.6]tricos-16-ene-3,6,9,19,22- pentone

CAS registry number:
128517-07-7

Molecular formula: $C_{24}H_{36}N_4O_6S_2$
Molecular weight: 540.71 g/mol



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
2315	V	Ben Venue Laboratories, Inc	Drug product manufacturing facility and equipment	3	Adequate	Dec. 14, 2008	See microbiology review
—	III	—	—	3	Adequate	Oct. 28, 2008 Sept. 20, 2006	Reviewed by Dr. Debasis Ghosh Reviewed by Dr. Kris Raman

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	51,810	IND for development
IND	63,573	IND for development

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	June 22, 2009	S. Ferguson
Pharm/Tox	Acceptable	Oct. 20, 2009	Alex Putman
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMEPA	pending	Aug. 5, 2009 Oct 15, 2009	Cathy A. Miller
EA	Categorical exclusion (see review)		Ying Wang
Microbiology	Acceptable	Aug. 3rd, 2009	Bryan S. Riley

The CMC Review for NDA 22-393

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing, and control perspective, this NDA is recommended for approval, pending receipt of final and acceptable container/carton labels for the drug product.

Please insert the following language into the action letter: "The approved expiration dating period is 36-months based on the submitted stability data for this drug product, as co-packaged in two separate single-use vials and when stored at 20°-25°C (68°-77°F); excursions permitted between 15°-30°C (59°-86°F).."

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

Drug substance romidepsin is a white (—— powder and is a new molecular entity.

Romidepsin is a bicyclic depsipeptide produced by traditional fermentation and purified by : Drug substance is stable at the storage condition of 25°C/60% RH. The proposed —— retest period is acceptable based on the provided stability data.

(2) Drug Product

Drug product ISTODAX is supplied as a kit containing two vials. ISTODAX (romidepsin) for injection is a sterile lyophilized white powder and is supplied in a single-use vial containing 10 mg romidepsin and 20 mg of the bulking agent, povidone, USP. Diluent for ISTODAX is a sterile clear solution and is supplied in a single-use vial

containing a 2-mL deliverable volume. Diluent for ISTODAX contains 80% (v/v) propylene glycol, USP and 20% (v/v) dehydrated alcohol, USP.

[ ] used in the drug product manufacturing and is removed during lyophilization process. The [ ] in the drug product is in the range of ——— 10 mg romidepsin. The applicant proposed acceptance criterion of —— /10 mg romidepsin for the drug product. This —— is not listed in the and there is no animal study done with this ——in the IV route of administration. Pharmacology/toxicology (Pharm/Tox) has been consulted for this issue. They have issued the opinion that [ ] in the drug product specification should be based on the level seen during the clinical trials, which was — /10 mg romidepsin. (please refer to Pharm/Tox review for additional details). The applicant accepted Pharm/Tox's recommendation and revised the acceptance criterion of ——— in the drug product to —— /10 mg romidepsin vial. b(4)

Drug product romidepsin is stable at the storage condition of 25°C/60% RH and the proposed expiry of 36 month is acceptable based on the stability data provided. Diluent is stable at the storage condition of 25°C/60% RH and the proposed expiry of 36 month is also acceptable based on the stability data provided. The expiry for the drug product ISTODAX (the co-packaged product) is 36 months when stored under the proposed conditions (25°C/60% RH).

B. Description of How the Drug Product is Intended to be Used

ISTODAX (romidepsin) for injection is indicated for treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy. The recommended dose of romidepsin is 14 mg/m^2 administered intravenously over a 4-hour period on days 1, 8 and 15 of a 28-day cycle. Cycles should be repeated every 28 days provided that the patient continues to benefit from and tolerates the therapy. ISTODAX must be reconstituted with the supplied diluent and then further diluted with 0.9% Sodium Chloride Injection, USP before intravenous infusion.

The applicant proposed, and is granted, a 36-month shelf life based on the submitted stability data for this drug product kit packaged in two separate single-use vials and when stored at 20°-25°C (68°-77°F); excursions permitted between 15°-30°C (59°-86°F).

C. Basis for Approvability or Not-Approval Recommendation

There was sufficient information in the NDA submission and subsequent amendments to evaluate the manufacturing process, control strategy, and analytical methods to ensure the quality of the drug product. An overall acceptable recommendation was received from the Office of Compliance, and there are no outstanding CMC deficiencies for this application. While there are several outstanding issues regarding revised container/carton labeling, as identified in the DMEPA review, the currently proposed labels are acceptable from a CMC standpoint.

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Ying Wang, PhD, CMC reviewer, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Sarah Pope Miksinski, PhD, Branch Chief, Branch V, ONDQA

C. CC Block: entered electronically in DFS

139 Page(s) Withheld

X Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Withheld Track Number: Chemistry Review Section- 1

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

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/s/

YING WANG
10/20/2009

Sarah Pope Miksinski
10/21/2009

Initial Quality Assessment
Branch V
Pre-Marketing Assessment and Manufacturing Science Division III
Office of New Drug Quality Assessment

OND Division:	Division of Drug Oncology Products
NDA:	22-393
Applicant:	Gloucester Pharmaceuticals, Inc.
Stamp date:	12-JAN-2009
PDUFA Date:	12-JUL-2009
Proposed Trade Name:	ISOTODAX for Injection
Established Name:	Romidepsin
Laboratory Code:	N/A
Dosage Form:	Lyophilized powder to be reconstituted for solution dosage form
Route of Administration:	Intravenous
Indication:	Treatment of cutaneous T-cell lymphoma (CTCL), including relief of pruritus
Related IND Number:	51,810 and 63,573

Pharmaceutical Assessment Lead: Haripada Sarker, Ph.D.

	YES	NO
ONDQA Fileability:	√	___
Draft Comments for 74-Day Letter:	√	___

Summary, Critical Issues and Comments

A. Summaries

Background Summary

NDA 22-393 is submitted under Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for ISOTODAX (romidepsin) Injection intended for treatment of cutaneous T-cell lymphoma (CTCL), including relief of pruritus, in patients who have received at least one prior systemic therapy. Romidepsin is an anti-neoplastic agent that has been identified as a novel histone deacetylase (HDAC) inhibitor. It is a new molecular entity. It has not been decided whether it is a priority or standard NDA. ISOTODAX (romidepsin) Injection is formulated as a sterile lyophilized powder for solution dosage form containing 10 mg/vial of romidepsin. It is supplied in a dual-pack configuration with a Diluent vial (80% Propylene Glycol, USP, and 20% Dehydrated Alcohol, USP; sterile) for use in reconstitution.

The intended approval for NDA 22-393 is based on a Phase 2, multi-center, open-label, single-arm, international study designed to assess the efficacy and safety of romidepsin in the patients with CTCL who had failed at least 1 prior systemic therapy. The investigational drug was studied by the Cancer Therapy Evaluation Program (CTEP) of the NCI and Astellas under IND 51,810 and 63,573. In April 2004, Gloucester Pharmaceuticals, Inc. (Gloucester) acquired the license to develop romidepsin from Astellas.

The CMC milestones during the drug development are the submission of the initial IND on May 7, 2002, the CMC pre-NDA meetings held on May 30, 2007, and the multidisciplinary pre-NDA meeting on May 7, 2008. There appears to be no CMC specific EOP-2 meeting under the IND file. At the May 30, 2007 Pre-NDA CMC meeting, FDA reviewed the comparability testing results for the commercial and clinical romidepsin drug substance, the proposed NDA specifications and shelf-life for drug substance, drug product, and the reconstitution diluent. Based on the data in the meeting package, the FDA agreed with Gloucester that the drug substance batches manufactured at the proposed commercial site and those used for clinical studies were comparable, provided that results for the comparative accelerated stability testing were supportive. These supportive accelerated stability data are summarized in the NDA. The report of the analytical comparability testing was submitted to IND 63,573 (SN0131; 5 November 2008) and is also included in the NDA.

Drug Substance Summary

Romidepsin is a bicyclic depsipeptide. ⌐

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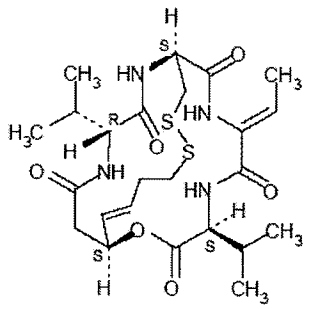

Figure 1. Romidepsin (MW=540.71 g/mole)

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b(4)

Romidepsin is produced by
using a strain of *Chromobacterium violaceum*, a naturally occurring soil bacterium that has been mutated to enhance production of romidepsin. Development and characterization of the bacterium strain *Chromobacterium violaceum* are described in section 3.2.S.2.6.2. Note that there was a strain change during the clinical studies, the strain — which will be used in the commercial process has also been used in the clinical studies and process validation.

b(4)

Drug substance for clinical trials was manufactured at Astellas Pharmaceuticals, Inc. (formerly Fujisawa Pharmaceuticals, Ltd.). Drug substance for commercial supply, including validation batches, is manufactured at ! _____ at a scale that is —— of the most recent batches manufactured by Astellas for clinical trial supplies. Over the course of

b(4)

development, there are some manufacturing process changes, and they are summarized in Figure 1 of Section 3.2.S.2.6.1. The applicant had submitted comparability testing plan for the commercial and clinical romidepsin drug substance, and the results for the comparability testing were submitted in the NDA, and they were discussed at the May 30, 2007 pre-NDA meeting. Preliminarily review of the comparability data suggested that commercial batches and the clinical batches were comparable. This also needs to be confirmed during the NDA review taking into the consideration of the newly submitted comparable accelerated stability data.

The drug substance specifications were established based on release and stability data from drug substance lots used in clinical studies, and the manufacturing capability for the intended commercial process and scale. The specifications appear to be typical for a small-molecule drug substance, and they are the same as, or tighter than, those for the clinical studies. The noncompendial analytical procedures used for testing romidepsin drug substance, including ——— related substances (organic impurities), and assay were validated, and the validation data were submitted. The HPLC method for assay is the same as the HPLC method used for related substances with an LOQ of —— b(4)

Batch analysis data for 12 lots of drug substance were presented. Out of those 12 lots, five were produced at the intended commercial site and scale, three of those 5 lots are validation and primary stability lots, and the rest 7 lots were used in the nonclinical, clinical studies and supportive stability studies. All test results conformed to the proposed specifications except two nonclinical lots which had total impurity levels (——— higher than the proposed acceptance criterion (NMT —). b(4)

Three lots of primary stability data for 18 month of long term (25°C/60% RH) and 6 month of accelerated conditions (40°C/75% RH) were included in the NDA. These 3 lots of drug substance were manufactured at the commercial site —— and scale. In addition, stability data for 4 supportive lots manufactured at Astellas were provided. The acceptance criteria for the stability studies are the same as those of the release testing specifications. The results demonstrated all specifications were met, with no significant change of impurity profiles under either log term or accelerated storage conditions. In addition, 36 months supportive stability data also conformed to specifications. The applicant proposed a —— retest date when stored at < 25°C in an HDPE container. b(4)

Drug Product Summary

Drug product is manufactured as a sterile, lyophilized powder containing 10 mg/vial romidepsin and 20 mg/vial Povidone, USP. It is supplied in a dual-pack configuration with a Diluent vial containing 80% Propylene Glycol, USP, and 20% Dehydrated Alcohol, USP to be used for reconstitution. All excipients are compendial except the component ——— in the drug product. Note that all drug product formulation development work was conducted prior to initiation of clinical studies and in parallel with the diluent development. Therefore, the formulation for both drug product and diluent remain unchanged throughout the clinical studies to the proposed commercial production. b(4)

Commercial drug product is manufactured by Ben Venue Laboratories, Inc. (BVL), which is also the manufacturer for all clinical batches. BVL is responsible for all aspects of drug product manufacturing including raw material testing as well as release and stability studies. The

manufacturing scale for the commercial drug product supply, including validation batches, is the same as that is used for the four most recent clinical batches. A typical batch size is : — b(4)
———————— Detailed manufacturing information is provided in the NDA. DMF (#2315) was submitted by BVL which includes information for the facility, and the qualification, and calibration of the sterilization equipment. An authorization letter to the BVL DMF is provided in Section 1.4.1.

Drug product is manufactured by using conventional : — processing which includes ⌜ b(4)
⌟ and lyophilization. The drug product vial is co-packaged with the diluent vial that is also manufactured by BVL using —— processing. Note that no reworking or reprocessing of the drug product is proposed.

A summary of the development of the drug product formulation and manufacturing process is provided in section 3.2.P.2. Romidepsin has been shown to be stable in the ⌜

b(4)

⌟

The drug product specifications were established based on release and stability data from drug product lots used in clinical studies, and manufacturing capability for the intended commercial process and scale. The specifications are also based on a maximum daily dose of 40 mg. The acceptance criteria appear to be typical for a small-molecule drug product formulated for injection dosage form, and they are the same as, or tighter than, those for the clinical studies.
⌜

b(4)

⌟

Batch analysis data from 15 lots of drug product produced at BVL were submitted. Out of those 15 lots, 9 lots were manufactured at the commercial scale and the rest are smaller scale development batches. The results demonstrated that all tests met the proposed commercial b(4)
specifications, and they appear to be comparable between the small scale clinical batches ⌜ ⌟ and the commercial scale batches ⌜ ⌟.

The primary stability studies are conducted per ICH Q1A (R2) at the intended long-term storage conditions of 25°C/60%RH, along with a 6-month accelerated conditions of 40°C/75% RH. Stability data from 9 lots of drug product manufactured at BVL using the commercial process were submitted, and they are identified by the applicant as being the primary stability lots, and are the basis to support the proposed shelf life of 36 month. Out of those 9 primacy stability lots,

six lots were manufactured at the intended commercial scale, and the other 3 lots were validation lots. The amount of primary stability data supporting the proposed storage and shelf-life of 36 months at 25°C/60%RH are 42 months for 3 lots, 24 months for 2 lots, 12 months for 1 lot, and 9 months for 3 validation lots. Since there many primary stability lots with various amount of data from 9 to 42 months, it is important for the reviewer to determine the most relevant primary stability lots to support the shelf life. Note that no statistical analysis has been performed on the submitted stability data. It would be the reviewer's decision whether statistical analysis of the stability data is necessary or not; and if the statistical consult should be requested.

Diluent for Romidepsin Drug Product

There is a separate section in the drug product section in module 3, which provides CMC information for the co-packaged diluent. The diluent for romidepsin drug product is a sterile solution composed of 80% v/v Propylene Glycol, USP, and 20% v/v Dehydrated Alcohol, USP. It is supplied in a — vial with a 2.0 mL fill and a USP recommended overfill of 0.15 mL, and contains no preservatives. Each diluent vial is intended for use in reconstituting a single vial of romidepsin lyophilized powder. It is manufactured by BVL using standard — processing technology. Release testing of the diluent includes the following attributes: appearance, identification, assay, volume in container, particular matter, bacterial endotoxins, and sterility. Batch analysis data from 13 batches of the diluent were provided. All tested have met the proposed commercial specification. Note that formulation, manufacturing process, container closure system, and analytical methods have remained unchanged during development. Stability studies were conducted per ICH Q1A (R2) using the same long term and accelerated conditions as those for the drug product. Three process validation lots manufactured by BVL were placed on stability as the primary stability lots. Twenty-four month long term and 6 month accelerated stability data were submitted to support the proposed expiry of 36 month stored at controlled room temperature (20 to 25°C with excursions permitted from 15 to 30°C).

b(4)

Manufacturing sites to request CGMP status:

Name and address	Registration #	Responsibility
	—	Production and release testing of drug substance; storage of future stability samples and stability testing
	—	Testing of first 5 production lots, including 3 validation lots manufactured by : — Alternate analytical testing site for future lots
	Not provided	Storage of stability samples for 3 primary/validation lots **Comment: No need to request EES inspection due to the nature of its responsibility**
	—	Storage of drug substance **Comment: No need to request EES inspection due to the nature of its responsibility**

b(4)

Name and address	Registration #	Responsibility
Ben Venue Laboratories, Inc. 300 Northfield Road Bedford, Ohio 44146	CFN 151925	Raw material testing, compounding, sterilization, —— filling, lyophilization, inspection, testing, labeling, packaging, and stability studies for both drug product and diluent
	——	Container closure leachables testing for the diluent

b(4)

B. Critical issues for review and recommendation

Drug Substance

a. The drug substance is ——————————. Appropriate and unique controls for the manufacturing process should be carefully assessed. During drug development the manufacturing process including the bacterial strain has been modified to improve the robustness of the process and quality of the drug substance. These changes along with the comparability data (also including accelerated stability data) should be assessed to determine whether they affect impurity profile of the drug substance.

b. Romidepsin drug substance is an optically active compound with 4 chiral centers. The presence of potential diastereomers as well as the capability of the HPLC method to separate them form romidepsin is studied in a peak purity study as agreed in the May 30, 2007 CMC specific pre-NDA meeting.

c. The applicant indicated that the HPLC method used to measure assay (and also used for related substances) is a stability indicating method and provided validation data to support the claim. This needs to be confirmed.

Drug Product

a. Since the diluent is formulated with two organic solvents, potential extractables and leachables were studied. The presence of leachables is also monitored in the diluent stability studies. The results of these studies should be carefully evaluated.

b. The proposed acceptance criterion for [ ]/vial, is based on the calculation of maximum allowable daily intake (ADI) of ———— using mice LD_{50} and the maximum daily dose. The acceptance of this approach should be evaluated and also consulted to the pharm/tox review team.

b(4)

c. Applicant has proposed 9 drug product lots as the primary stability lots. Although all 9 lots were manufactured with the same formulation and a process that is representative of the commercial process, 6 of them are clinical lots and the rest 3 are validation lots, and they were manufactured at different scales, and using different drug substance lots (commercial site vs non-commercial site). Data from these 9 lots were used to support the proposed shelf life. How similar and/or representative of these lots to the proposed commercial lots should be determined when evaluate and grant the proposed shelf life.

C. Comments for 74-day Letter:

1. The proposed container/carton labels cannot be located in your NDA submission. Submit the proposed container/carton labels.

D. Recommendation for fileability: Fileable

Fileability Template

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	√		Except for one facility that is responsible for storage of stability samples for 3 primary/validation lots
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?	√		Although stability data were provided, no statistical analysis of the data has been performed.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		
11	Have draft container labels been provided?		√	Draft container labels will be requested in the 74 day letter.
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?		√	
16	Have all consults been identified and initiated? (bolded items to be handled by ONDQA PM)	√ √		**Microbiology** Pharm/Tox Biopharm Statistics (stability) OCP/CDRH/CBER LNC DMEPA/ODS **EER**

Have all DMF References been identified? Yes (√) No ( )

DMF Number	Holder	Description	LOA Included
2315 (Type V)	Ben Venue Laboratories, Inc.	Sterilization validation	Yes
			Yes

b(4)

Recommendation for Team Review:

This NDA appears to be a relatively straightforward NDA with regard to the CMC information included. However, assessment of drug substance manufacturing and controls may require some expertise since the drug substance is produced by [redacted] Review of this NDA can be easily conducted by a single reviewer with the consult to appropriate expertise in [redacted] as considered appropriate and necessary, and the team approach is not recommended for this NDA.

Xiao-Hong Chen, Ph.D.
Pharmaceutical Assessment Lead

13-FEB-2009
Date

Sarah C. Pope, Ph.D.
Branch Chief

18-FEB-2009
Date

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/s/

Xiao Hong Chen
2/18/2009 04:27:39 PM
CHEMIST

Sarah Pope
2/23/2009 02:03:49 PM
CHEMIST

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 22393/000	**Action Goal:**	
S' Date:	12-JAN-2009	**District Goal:**	13-SEP-2009
Regulatory:	12-NOV-2009		
Applicant:	GLOUCESTER PHARMS	**Brand Name:**	ROMIDEPSIN FOR INFUSION
	1 BROADWAY 14TH FLOOR	**Estab. Name:**	
	CAMBRIDGE, MA 02142	**Generic Name:**	ROMIDEPSIN FOR INFUSION
Priority:	1	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	150	001; POWDER, FOR INJECTION SOLUTION, LYOPHILIZED; ROMIDEPSIN; 10MG	

Application Comment: ACCORDING TO THE CLINICAL REVIEW DIVISION, THIS NDA MAY BE CLASSIFIED AS A PRIORITY REVIEW, WHCIH WILL HAVE A GOAL DATE OF JULY 12, 2009. NOTE THAT DRUG PRODUCT IS PROVIDED AS A DUEL PACK SYSTEM WHCIH CONTAINS A DP VIAL COPACKAGED WITH A DILUENT VIAL. BVL IS ALSO RESPONSIBLE FOR THE MANUFACTURING AND TESTING OF THE DILUENT, WHICH INCLUDES RAW MATERIAL TESTING, COMPOUNDING, STERILIZATION, —— FILLING, PACKAGING, RELEASE AND STABILITY TESTING. (on 13-FEB-2009 by X. CHEN () 301-796-1337)

b(4)

FDA Contacts:	D. MESMER	Project Manager	(HFD-800)	301-796-4023
	Y. WANG	Review Chemist		301-796-1479
	H. SARKER	Team Leader	(HFD-150)	301-796-1747

Overall Recommendation:	ACCEPTABLE	on 22-JUN-2009	by S. FERGUSON	(HFD-322)	301-796-3247

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 1519257 **FEI:** 1519257

BEN VENUE LABORATORIES INC

300 NORTHFIELD RD
BEDFORD, OH 441464650

DMF No: 2315 **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

Estab. Comment: FOR DRUG PRODUCT PERFORMS RAW MATERIAL TESTING, COMPOUNDING, STERILIZATION, ——— FILLING, LYOPHILIZATION,INSPECTION,TESTING,LABELING,PACKAGING, AND STABILITY STUDIES. NOTE THAT DRUG PRODUCT IS PROVIDED AS A DUEL PACK SYSTEM WHICH CONTAINS A DP VIAL COPACKAGED WITH A DILUENT VIAL. BVL IS ALSO RESPONSIBLE FOR THE MANUFACTURING AND TESTING OF THE DILUENT, WHICH INCLUDES RAW MATERIAL TESTING, COMPOUNDING, STERILIZATION, ——— FILLING, PACKAGING, RELEASE AND STABILITY TESTING. PLEASE CHECK WITH THE REVIEWER FOR ANY POTENTIAL PROBLEM DISCOVERED DURING REVIEW BEFORE INSPECTION TRIP.
(on 13-FEB-2009 by D. MESMER (HFD-800) 301-796-4023)

b(4)

Profile: SMALL VOLUME PARENTERAL, LYOPHILIZED **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	13-FEB-2009				CHENX
SUBMITTED TO DO	14-FEB-2009	Product Specific			KIEL
DO RECOMMENDATION	22-JUN-2009			ACCEPTABLE	KCULVER
CIN-DO RECOMMENDS APPROVAL BASED ON FILE AND ANDA REVIEW AND RECENT COMPREHENSIVE GMP INSPECTION FROM 4/6 - 5/13/09 WHICH IS VAI AND COVERED LYOPHILIZATION.				BASED ON FILE REVIEW	
OC RECOMMENDATION	22-JUN-2009			ACCEPTABLE	FERGUSONS
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** [redacted] **FEI:** [redacted]

[redacted]

b(4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Estab. Comment: FOR DRUG SUBSTANCE PERFORMS RAW MATERIAL TESTING [redacted], PACKAGING, LABELING, ANALYTICAL RELEASE AND STABILITY TESTING. STORAGE OF FUTURE STABILITY SAMPLES. PLEASE CHECK WITH THE REVIEWER FOR ANY POTENTIAL PROBLEM DISCOVERED DURING REVIEW BEFORE INSPECTION TRIP.
(on 10-FEB-2009 by D. MESMER (HFD-800) 301-796-4023)

Profile: [redacted] **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	13-FEB-2009				CHENX
SUBMITTED TO DO	17-FEB-2009	Product Specific			ADAMSS
DO RECOMMENDATION	19-FEB-2009			ACCEPTABLE	JOHNSONE
				BASED ON FILE REVIEW	
OC RECOMMENDATION	25-FEB-2009			ACCEPTABLE	ADAMSS
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** ——— **FEI:** ———

———

b(4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Estab. Comment:

FOR DRUG SUBSTANCE PERFORMS RELEASE AND STABILITY TESTING OF FIRST 5 PRODUCTION LOTS(INCLUDING 3 VALIDATION LOTS); ALTERNATE ANALYTICAL TESTING SITE FOR FUTURE LOTS. PLEASE CHECK WITH THE REVIEWER FOR ANY POTENTIAL PROBLEM DISCOVERED DURING REVIEW BEFORE INSPECTION TRIP.
(on 10-FEB-2009 by D. MESMER (HFD-800) 301-796-4023)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	13-FEB-2009				CHENX
OC RECOMMENDATION	17-FEB-2009			ACCEPTABLE	ADAMSS
				BASED ON PROFILE	