CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206256Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 206256 SUPPL # HFD # 161

Trade Name Beleodaq™ for Injection

Generic Name belinostat

Applicant Name Spectrum Pharmaceuticals, Inc.

Approval Date, If Known Approximately 06/27/14

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(1)

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

YES ☒ NO ☐

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

N/A

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

N/A

d) Did the applicant request exclusivity?

YES ☐ NO ☒

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

N/A

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

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

1. Single active ingredient product.

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

YES ☐ NO ☒

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

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

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

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

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

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

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

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

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

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

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

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

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

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

interest provided substantial support for the study?

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

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

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

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form:
Virginia Kwitkowski, MS, RN, ACNP-BC, Clinical Team Leader
Hyon-Zu Lee, PharmD, Clinical Reviewer
Jessica Boehmer, MBA, Regulatory Project Manager

Date: June 11, 2014

Name of Office/Division Director signing form: Edvardas Kaminskas, MD

Title: Deputy Director, Division of Hematology Products

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

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

/s/

JESSICA L BOEHMER
06/13/2014

EDVARDAS KAMINSKAS
06/13/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 206256 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Beleodaq Established/Proper Name: belinostat Dosage Form: intravenous (IV) infusion		Applicant: Spectrum Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Jessica Boehmer		Division: Division of Hematology Products

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

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

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

❖ Actions	
• Proposed action • User Fee Goal Date is August 9, 2014	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only): NME (under the Program)
(confirm chemical classification at time of approval)

☒ Fast Track
☐ Rolling Review
☒ Orphan drug designation
☐ Breakthrough Therapy designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

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

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

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

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

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other - Burst
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Version: 5/14/2014

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action and date: Approval July 3, 2014
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	March 16, 2014 March 4, 2014
❖ Labeling reviews *(indicate dates of reviews)*	RPM: February 4, 2014 DMEPA: April 3, 2014 DMPP/PLT (DRISK): May 16, 2014 OPDP: May 12, 2014 SEALD: ☒ None CSS: ☒ None Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	February 4, 2014 ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included June 13, 2014
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: Orphan Designation	N/A, Orphan Designation
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	June 17,13, 12, and 11, 2014; May 23, 15 (2), 14 (2), and 13, 2014; April 16, 15, and 1, 2014; March 14 and 12, 2014; February 26 (3), 21, 20, 11, and 5, 2014; January 28, 27, and 9, 2014; and September 4, 2008 (SPA).
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	June 11, 2014
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	May 29, 2014
• EOP2 meeting *(indicate date of mtg)*	November 29, 2007
• Mid-cycle Communication *(indicate date of mtg)*	March 17, 2014
• Late-cycle Meeting *(indicate date of mtg)*	June 4, 2014
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	PMR Discussion: April 11, 2014
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	July 2, 2014
Division Director Summary Review *(indicate date for each review)*	June 12, 2014
Cross-Discipline Team Leader Review *(indicate date for each review)*	June 6, 2014
PMR/PMC Development Templates *(indicate total number)*	Clinical: June 16, 2014 Clin Pharm: June 16, 2014
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review Cosigned May 16, 2014 Review
• Clinical review(s) *(indicate date for each review)*	Review: May 16, 2014 Filing: January 22, 2014
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See Clinical Review, Page 22, May 16, 2014

❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	N/A N/A May 8, 2014
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	June 4, 2014; May 16, 2014
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review Cosigned May 19, 2014 Review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review Cosigned May 19, 2014 Review
Statistical Review(s) *(indicate date for each review)*	Review: May 19, 2014 Filing: January 23, 2014
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review Cosigned May 14, 2014 Review
Clinical Pharmacology review(s) *(indicate date for each review)*	Review: May 14, 2014 QT-IRT: April 8, 2014 Filing: January 29, 2014
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	May 22, 2014
• Supervisory Review(s) *(indicate date for each review)*	May 12, 2014
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	Review: April 30, 2014 Filing: January 16, 2014
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ No separate review
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ No separate review Cosigned May 7, 2014 Review
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	Review: May 7, 2014 Filing: January 29, 2014
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	Review: May 12, 2014 Filing: January 24, 2014
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See Product Quality Review, Page 63, May 7, 2014
☐ Review & FONSI *(indicate date of review)*	N/A
☐ Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: February 25, 2014 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER (date of most recent TB-EER must be within **30 days** of action date) *(original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☒ Requested ☐ Not yet requested ☐ Not needed (per review)

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

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	**N/A**
• Finalize 505(b)(2) assessment	**N/A**
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	N/A (Orphan Designation)
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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/s/

JESSICA L BOEHMER
07/09/2014

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Tuesday, June 17, 2014 3:35 PM
To: 'Anil Hiteshi'
Cc: Boehmer, Jessica
Subject: Officially submit agreement to PMR #1 edit - NDA 206256

Importance: High

Dear Anil,

I confirm receipt of the official submissions of final labeling and the proposed PMRs for Beleodaq (belinostat) for Injection, NDA 206256.

The Agency has proposed an edit to the description of PMR #1 to correct a grammatical error, as below:

> Establish the optimal safe dose of belinostat in combination with the cyclophosphamide/vincristine/doxorubicin/prednisone (CHOP) regimen. Perform a Phase 1 dose-finding trial of belinostat plus CHOP for the treatment of patients with peripheral T-cell lymphoma (PTCL). Enroll a sufficient number of patients to characterize the safety (b) (4) of belinostat in combination with the CHOP regimen. Submit a complete study report with all supporting datasets.

Please officially submit an amendment to NDA 206256 that you agree with the revised description text proposed for PMR #1.

Thank you,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9849 (fax)

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/s/

JESSICA L BOEHMER
06/17/2014

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Friday, June 13, 2014 2:01 PM
To: 'Anil Hiteshi'
Subject: FDA Proposed Revisions to PI- minor format changes : NDA 206256 - Beleodaq (belinostat) for Injection
Attachments: Final FDA-PI Edits Beleodaq-redline-pi-2014-06-13.doc

Importance: High

Dear Anil,

Please see attached revised draft of the **PI for NDA 206256 for Beleodaq (belinostat) for Injection. The Agency proposes the attached minor formatting edits.**

Please review the Agency's changes/comments and do the following to the same draft:

- - Accept any changes that you agree with
- - Edit over the ones that you do not agree with **(do not reject any changes that the FDA proposed)**
- - Make revisions or accept revisions requested in the comments section

If you agree with the attached proposed edits, please accept changes and submit the PI as final labeling. Please email me to let me know once you have submitted the final labeling.

Thank you,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(301) 796-5357 (phone)
(301) 796-9849 (fax)

11 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JESSICA L BOEHMER
06/13/2014

MEMORANDUM OF TELECONFERENCE

Teleconference Date: June 11, 2014

Application Number: NDA 206256
Product Name: Beleodaq (belinostat) for Injection
Sponsor/Applicant Name: Spectrum Pharmaceuticals, Inc.

Subject: Proposed PMRs #6 and #7 and possible early NDA action

FDA Participants

Division of Hematology Products (DHP)
Virginia Kwitkowski, MS, RN, ACNP-BC, Clinical Team Leader
Toni-Ann Cox, Regulatory Project Manager
Jessica Boehmer, MBA, Senior Regulatory Project Manager

Office of Clinical Pharmacology (OCP)
Julie Bullock, PharmD, Clinical Pharmacology Team Leader
Rosane Charlab Orbach, PhD, Acting Team Leader, Genomics and Targeted Therapy Group
Sarah Dorff, PhD, Genomics Reviewer, Genomics and Targeted Therapy Group

Sponsor/Applicant Participants

Spectrum Pharmaceuticals, Inc.
Lee F. Allen, MD, PhD, Chief Medical Officer
Guru Reddy, PhD, Vice President, Preclinical Research and Development
Gajanan Bhat, PhD, Executive Director, Biostatistics and Data Management
Mi Rim Choi, MD, Director, Clinical Research
Anil K. Hiteshi, RAC, Vice President, Global Regulatory Affairs
Kevin Matchett, Director, Project Management

1.0 BACKGROUND:

NDA 206256 is currently under review by DHP. The teleconference was scheduled to alert the Applicant of a potential early action and to discuss outstanding Clinical Pharmacology PMRs 6 & 7.

2.0 DISCUSSION:

The Clinical Pharmacology team indicated (b) (4) as genotype information is needed. The Agency clarified that PMR #7 could be included in an ongoing or future study (the Applicant could include enrollment in PMR #6 to address PMR #7).

The Agency informed the Applicant that there is a possibility for early action. The Applicant indicated that they have the 3 validation batches manufactured and they are almost ready with labeling (upon agreement).

3.0 ACTION ITEMS:

Spectrum will send their proposed edits to the PI and PMRs.

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/s/

JESSICA L BOEHMER
06/12/2014

Boehmer, Jessica

From: Anil Hiteshi <anil.hiteshi@sppirx.com>
Sent: Wednesday, June 11, 2014 3:53 PM
To: Boehmer, Jessica
Subject: RE: FDA Proposed Revisions to PI NDA 206256 - Beleodaq (belinostat) for Injection - response due June 16
Attachments: 2014-06-11-att-pmr-beleodaq.docx; Final FDA Edits Beleodaq-redline-pi-2014-06-11-sppi-cmnts.doc

Follow Up Flag: Follow up
Flag Status: Flagged

Dear Jessica,

It was a pleasure speaking with you and your team this morning. Once again, Spectrum greatly appreciates the Agency's dialog and collaboration.

As we discussed, we are in agreement on all the proposed PMRs, and have acknowledged our acceptance of them in the attached document.

We have also attached the updated package insert in which we have accepted all the proposed FDA changes with the exception of (b) (4)

(b) (4)

So that we can be well prepared, can you please give us a general timeline for the possible early action on the Beleodaq NDA? Please let me know if you have any questions or need any additional information.

Thank you again for your kind assistance.

Best regards,

Anil

Anil K. Hiteshi, RAC
Vice President, Global Regulatory Affairs
Spectrum Pharmaceuticals
157 Technology Drive | Irvine, CA 92618
T: (949) 743-9228 | F: (949) 788-6708
anil.hiteshi@sppirx.com | www.sppirx.com

SPECTRUM PHARMACEUTICALS
Redefining Cancer Care

From: Boehmer, Jessica [mailto:Jessica.Boehmer@fda.hhs.gov]
Sent: Wednesday, June 11, 2014 7:32 AM
To: Anil Hiteshi
Cc: Boehmer, Jessica
Subject: FDA Proposed Revisions to PI NDA 206256 - Beleodaq (belinostat) for Injection - response due June 16
Importance: High

Dear Anil,

Please see attached revised draft of the **PI for NDA 206256 for Beleodaq (belinostat) for Injection.**

Please review the Agency's changes/comments and do the following to the same draft:

- - Accept any changes that you agree with.
- - Edit over the ones that you do not agree with **(do not reject any changes that the FDA proposed).**
- - Make revisions requested in the comments section.

After you have made the changes, please send me the revised **tracked changes** document (Word version). Do not officially submit the revised PI at this time.

Please provide a revised PI to me by **3:00 PM ET on Monday, June 16, 2014.**

Thank you,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(301) 796-5357 (phone)
(301) 796-9849 (fax)

PMR #1 Description

Establish the optimal safe dose of belinostat in combination with the cyclophosphamide/vincristine/doxorubicin/prednisone (CHOP) regimen. Perform a Phase 1 dose finding trial of belinostat plus CHOP for the treatment of patients with peripheral T-cell lymphoma (PTCL). Enroll a sufficient number of patients to characterize the safety of the combination of belinostat in combination with the CHOP regimen. Submit a complete study report with all supporting datasets.

PMR #1 Schedule Milestones

Final Protocol Submission:	Completed
Trial Completion:	June 2015
Final Report Submission:	April 2016

PMR #2 Description

Characterize the comparative efficacy and safety of Beleodaq when used in combination with a treatment regimen such as CHOP versus CHOP alone or pralatrexate plus CHOP versus CHOP alone for the initial therapy of patients with PTCL. Perform a confirmatory, prospective randomized (1:1:1) trial of previously untreated patients with PTCL, with progression free survival (PFS) as the primary efficacy endpoint. Enroll a sufficient number of patients to characterize the efficacy and safety of each drug added to CHOP, versus CHOP alone. The PFS endpoint should be determined by a blinded independent review committee. PFS analysis should be performed when the trial has experienced the planned number of events necessary for trial completion. Using the same data cutoff date as the PFS analysis, perform an interim analysis of overall survival. Submit a complete study report with all supporting datasets.

PMR #2 Schedule Milestones

Preliminary Protocol Submission:	July 2014
Final Protocol Submission:	December 2015
Accrual of 25% of Subjects:	April 2017
Accrual of 50% of Subjects:	April 2018
Accrual of 75% of Subjects:	April 2019
Trial Completion:	January 2020
Final Report Submission:	January 2021

PMR #3 Description

Characterize the mass balance information for Beleodaq. Submit the final clinical trial report for the ongoing human mass balance trial (Protocol SPI-BEL-12-103) designed to evaluate the excretion route of belinostat in humans. Submit a complete study report with all supporting datasets.

PMR #3 Schedule Milestones

Final Protocol Submission:	completed
Trial Completion:	December 2014
Final Report Submission:	March 2015

PMR #4 Description

Characterize the PK and safety of belinostat in the presence of hepatic impairment. Submit the final clinical trial report for the ongoing hepatic impairment trial (Protocol CTEP #8846) that is designed to evaluate the influence of hepatic impairment on the PK and safety of belinostat. Submit a complete study report with all supporting datasets.

PMR #4 Schedule Milestones

Final Protocol Submission:	completed
Trial Completion:	December 2015
Final Report Submission:	March 2016

PMR #5 Description

Characterize the PK and safety of belinostat in the presence of renal impairment. Conduct a clinical trial in patients with varying degrees of renal impairment to evaluate the pharmacokinetic and safety of belinostat patients with impaired renal function. The trial should be conducted for sufficient duration in order to evaluate safety following multiple dose administration. Submit a complete study report with all supporting datasets.

PMR #5 Schedule Milestones

Final Protocol Submission:	December 2014
Trial Completion:	December 2015
Final Report Submission:	March 2016

PMR #6 Description

Characterize the PK of belinostat in the presence of strong UGT1A1 inhibitors. Conduct a clinical trial evaluating the influence of strong UGT1A1 inhibitors on the pharmacokinetics of belinostat in patients with cancer. Submit a complete study report with all supporting datasets.

PMR #6 Schedule Milestones

Final Protocol Submission:	December 2014
Trial Completion:	December 2015
Final Report Submission:	March 2016

PMR #7 Description

Evaluate the safety and pharmacokinetics of belinostat in patients with wild-type, heterozygous, and homozygous UGT1A1*28 genotypes. The evaluations should be conducted for sufficient duration and in a sufficient number of subjects in order to evaluate safety following multiple dose administration. Submit a complete study report with all supporting datasets.

PMR #7 Schedule Milestones

Final Protocol Submission:	December 2014
Trial Completion:	December 2015
Final Report Submission:	March 2016

PMR #8 Description

Conduct an *in vitro* study to determine the exact contributions of UGT1A1, CYP3A4, CYP2C9, and CYP2A6 in the biotransformation of belinostat. Submit a complete study report with all supporting datasets.

PMR #8 Schedule Milestones

Final Protocol Submission:	December 2014
Study Completion:	July 2015
Final Report Submission:	September 2015

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/s/

JESSICA L BOEHMER
06/12/2014

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Thursday, June 12, 2014 1:38 PM
To: Anil Hiteshi
Cc: Boehmer, Jessica
Subject: FDA Proposed Revisions to PI : NDA 206256 - Beleodaq (belinostat) for Injection - response due June 16
Attachments: Final FDA Edits Beleodaq-redline-pi-2014-06-12-sppi-cmnts Section 12 1 edits.doc

Importance: High

Dear Anil,

Please see attached revised draft of the **PI for NDA 206256 for Beleodaq (belinostat) for Injection.**

Please review the Agency's changes/comments and do the following to the same draft:

- - Accept any changes that you agree with
- - Edit over the ones that you do not agree with **(do not reject any changes that the FDA proposed)**
- - Make revisions requested in the comments section

After you have made the changes, please send me the revised **tracked changes** document (Word version). Do not officially submit the revised PI at this time.

Please provide a revised PI to me via email by **3:30 PM ET on Monday, June 16, 2014.**

Thank you,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(301) 796-5357 (phone)
(301) 796-9849 (fax)

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/s/

JESSICA L BOEHMER
06/12/2014

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Wednesday, June 11, 2014 10:32 AM
To: Anil Hiteshi
Cc: Boehmer, Jessica
Subject: FDA Proposed Revisions to PI NDA 206256 - Beleodaq (belinostat) for Injection - response due June 16
Attachments: FDA Edits Beleodaq-redline-pi-2014-06-11_.doc

Importance: High

Dear Anil,

Please see attached revised draft of the **PI for NDA 206256 for Beleodaq (belinostat) for Injection.**

Please review the Agency's changes/comments and do the following to the same draft:

- - Accept any changes that you agree with.
- - Edit over the ones that you do not agree with **(do not reject any changes that the FDA proposed).**
- - Make revisions requested in the comments section.

After you have made the changes, please send me the revised **tracked changes** document (Word version). Do not officially submit the revised PI at this time.

Please provide a revised PI to me by **3:00 PM ET on Monday, June 16, 2014.**

Thank you,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(301) 796-5357 (phone)
(301) 796-9849 (fax)

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/s/

JESSICA L BOEHMER
06/11/2014

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Friday, May 23, 2014 2:17 PM
To: Anil Hiteshi (anil.hiteshi@sppirx.com)
Cc: Boehmer, Jessica
Subject: FDA Proposed Revisions to PI & PPI: NDA 206256 - Beleodaq (belinostat) for Injection - response due May 28
Attachments: Beleodaq_PI_FDA_Response_23May2014.doc; Belinostat_PPI_FDA_Edits_PPI_23May 2014.docx

Importance: High

Dear Anil,

Please see attached revised draft of the **PI and Patient Labeling for NDA 206256 for Beleodaq (belinostat) for Injection.**

Please review the Agency's changes/comments and do the following to the same draft:

- - Accept any changes that you agree with
- - Edit over the ones that you do not agree with **(do not reject any changes that the FDA proposed)**
- - Make revisions requested in the comments section

After you have made the changes, please send me the revised **tracked changes** document (Word version). Do not officially submit the revised PI or PPI at this time.

Please provide a revised PI and PPI to me by close of business on **Wednesday, May 28, 2014.**

These are the Agency's preliminary revisions, and there may be additional proposed revisions during continued labeling discussions.

Thank you,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(301) 796-5357 (phone)
(301) 796-9849 (fax)

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/s/

JESSICA L BOEHMER
05/23/2014

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Thursday, May 15, 2014 4:16 PM
To: Anil Hiteshi (anil.hiteshi@sppirx.com)
Cc: Boehmer, Jessica
Subject: Additional PMRs for Beleodaq (belinostat) for Injection: NDA 206256 - response due June 2

Importance: High

Dear Anil,

Please reference your NDA for Beleodaq (belinostat) for Injection, NDA 206256, submitted December 8, 2014 and received December 9, 2014.

As we continue our review of your Application, our normal policy is to consider post-marketing studies and labeling at this time, so that they can be completed in advance of any action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs) based on the data available to date. We may have additional PMRs/PMCs later. These brief descriptions of the necessary studies/trials are intended to describe the main objective and trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. It is also necessary for you to provide schedule milestone dates as indicated.

Please respond regarding the 2 PMRs sent May 14, 2014 and the following 6 PMRs by email to me by **4:00 PM ET, June 2, 2014**.

We are available to discuss by teleconference, if needed.

Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR and PMC studies/trials description to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial.
Final PMR designation numbers will be assigned later.

NDA #	206256
Product Name:	BELEODAQ (belinostat) for injection
PMR Description:	Characterize the mass balance information for Beleodaq. Submit the final clinical trial report for the ongoing human mass balance trial (Protocol SPI-BEL-12-103) designed to evaluate the excretion route of belinostat in humans. Submit a complete study report with all supporting datasets.

PMR Schedule Milestones:	Final Protocol Submission:	completed
	Trial Completion:	December 2014
	Final Report Submission:	March 2015

NDA #	206256
Product Name:	BELEODAQ (belinostat) for injection
PMR Description:	Characterize the PK and safety of belinostat in the presence of hepatic impairment. Submit the final clinical trial report for the ongoing hepatic impairment trial (Protocol CTEP #8846) that is designed to evaluate the influence of hepatic impairment on the PK and safety of belinostat. Submit a complete study report with all supporting datasets.

PMR Schedule Milestones:	Final Protocol Submission:	completed
	Trial Completion:	December 2014
	Final Report Submission:	March 2015

NDA #	206256
Product Name:	BELEODAQ (belinostat) for injection
PMR Description:	Characterize the PK and safety of belinostat in the presence of renal impairment. Conduct a clinical trial in patients with varying degrees of renal impairment to evaluate the pharmacokinetic and safety of belinostat patients with impaired renal function. The trial should be conducted for sufficient duration in order to evaluate safety following multiple dose administration. Submit a complete study report with all supporting datasets.

PMR Schedule Milestones:	Final Protocol Submission:	December 2014
	Trial Completion:	December 2015
	Final Report Submission:	March 2016

NDA #	206256
Product Name:	BELEODAQ (belinostat) for injection
PMR Description:	Characterize the PK of belinostat in the presence of strong UGT1A1 inhibitors. Conduct a clinical trial evaluating the influence of strong UGT1A1 inhibitors on the pharmacokinetics of belinostat in patients with cancer. Submit a complete study report with all supporting datasets.

PMR Schedule Milestones:	Final Protocol Submission:	December 2014
	Trial Completion:	December 2015
	Final Report Submission:	March 2016

NDA #	206256
Product Name:	BELEODAQ (belinostat) for injection

PMR Description:	Evaluate the safety and pharmacokinetics of belinostat in patients with wild-type, heterozygous, and homozygous UGT1A1*28 genotypes. The evaluations should be conducted for sufficient duration and in a sufficient number of subjects in order to evaluate safety following multiple dose administration. Submit a complete study report with all supporting datasets.

PMR Schedule Milestones:	Final Protocol Submission:	December 2014
	Trial Completion:	December 2015
	Final Report Submission:	March 2016

NDA #	206256
Product Name:	BELEODAQ (belinostat) for injection
PMR Description:	Conduct an *in vitro* study to determine the exact contributions of UGT1A1, CYP3A4, CYP2C9, and CYP2A6 in the biotransformation of belinostat. Submit a complete study report with all supporting datasets.

PMR Schedule Milestones:	Final Protocol Submission:	December 2014
	Study Completion:	July 2015
	Final Report Submission:	Sept 2015

Some things you can do to expedite this process:

1. For labeling and PMR/PMCs, reply to our drafts ASAP, and be sure to send the RPM a courtesy copy by email. Reply with your edits in a WORD document that you submit by email as well as to the document room. Use track changes to show YOUR edits. ACCEPT all of the track changes edits of ours with which you agree. You may provide annotation within the PI or, if extensive, in a separate document.

2. Assuming, and following a favorable action, you will then be submitting protocols intended to address the objectives of the PMRs agreed upon. We ask the following:

a. For any new studies, it is necessary to submit the protocol for DHP review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol and DHP has advised you that the protocol is judged acceptable to address the PMR/PMC. A fulfillment decision requires review.

b. Send the RPM an email courtesy copy of the draft versions, in WORD, as well as to the EDR officially. Again, for iterations, accept track changes sent to you that you agree with, and only return to us YOUR edits in track changes.

c. It is critical that you advise, prominently, both with the email and cover letter to the EDR that the protocol you are sending is to address a SPECIFIC POST MARKETING REQUIREMENT OR COMMITMENT (WITH THE PMR NUMBER). This helps the document room and us code the submission properly. All protocol submissions are made to the IND.

Thank you,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(301) 796-5357 (phone)
(301) 796-9849 (fax)

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/s/

JESSICA L BOEHMER
05/15/2014

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Wednesday, May 14, 2014 5:50 PM
To: Anil Hiteshi (anil.hiteshi@sppirx.com)
Cc: Boehmer, Jessica
Subject: FDA Proposed Revisions to Carton/Container: NDA 206256 - Beleodaq (belinostat) for Injection - response due May 16
Attachments: FDA_Proposed_Edits_NDA_206256_PI_13May2014.doc

Importance: High

Dear Anil,

Please reference new NDA 206256 for Beleodaq (belinostat) for Injection. Please also reference your amendment dated May 2, 2014, containing revised Carton and Container Labeling for NDA 206256 for Beleodaq (belinostat) for Injection.

Please see the additional comment, below, regarding the Carton and Container Labeling:

The carton and vial statements regarding storage time limit for the reconstituted solution should be changed from (b) (4) to 12 hours to correspond with the revised storage period specified in the PI:

Label	Initial	Revised
Carton	Reconstituted solution must be used within (b) (4) hours.	Reconstituted solution must be used within **12** hours.
Vial	Use within (b) (4) hours after reconstitution.	Use within **12** hours after reconstitution.

Please provide revised carton and container labels by close of business on Friday, May 16, 2014.

Kind regards,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OND/OHOP
(301) 796-5357 (phone)
(301) 796-9849 (fax)

From: Boehmer, Jessica
Sent: Tuesday, May 13, 2014 4:47 PM
To: Anil Hiteshi (anil.hiteshi@sppirx.com)
Cc: Boehmer, Jessica
Subject: FDA Proposed Revisions to PI & Carton/Container Comments: NDA 206256 - Beleodaq (belinostat) for Injection - response due May 16
Importance: High

Dear Anil,

Please see attached revised draft of the **PI for NDA 206256 for Beleodaq (belinostat) for Injection.**

Please review the Agency's changes/comments and do the following to the same draft:

- - Accept any changes that you agree with
- - Edit over the ones that you do not agree with **(do not reject any changes that the FDA proposed)**
- - Make revisions requested in the comments section

After you have made the changes, please send me the revised **tracked changes** document (Word version). Do not officially submit the revised PI at this time.

Please provide a revised PI to me by close of business on **Friday, May 16, 2014.**

These are the Agency's preliminary revisions, and there may be additional proposed revisions during continued labeling discussions. FDA comments on the proposed Patient Labeling will be forthcoming.

Please also reference your amendment dated May 2, 2014, containing revised **Carton and Container Labeling** for **NDA 206256 for Beleodaq (belinostat) for Injection.**

Container Label
1). The statement "Further dilution with Sodium Chloride Injection, 0.9% is required" appears to blend in with other information on the side panel. We recommend making this statement more prominent by bolding and placing on the principal display panel if space permits. This can be achieved by decreasing the prominence of the "Rx only" statement by moving this statement to the side panel and making it less prominent.

2) The "Rx only" statement still appears more prominent than the established name of the product and creates clutter. Therefore, decrease the prominence of that statement by reducing its size and possibly moving to the side panel.

Carton Labeling
1). Increase the prominence of the statement "Further dilution with Sodium Chloride Injection, 0.9% is required" by increasing font size, bolding, and placing on the other side panel (e.g., on the side panel that contains the usual dosing statement).

Please provide revised carton and container labels by close of business on **Friday, May 16, 2014.**

Thank you,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(301) 796-5357 (phone)
(301) 796-9849 (fax)

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/s/

JESSICA L BOEHMER
05/14/2014

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Wednesday, May 14, 2014 5:39 PM
To: Anil Hiteshi (anil.hiteshi@sppirx.com)
Cc: Boehmer, Jessica
Subject: PMRs for Beleodaq (belinostat) for Injection: NDA 206256

Importance: High

Dear Anil,

Please reference your NDA for Beleodaq (belinostat) for Injection, NDA 206256, submitted December 8, 2014 and received December 9, 2014.

As we continue our review of your Application, our normal policy is to consider post-marketing studies and labeling at this time, so that they can be completed in advance of any action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs) based on the data available to date. We may have additional PMRs/PMCs later. These brief descriptions of the necessary studies/trials are intended to describe the main objective and trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. It is also necessary for you to provide schedule milestone dates as indicated. We consider the proposed milestone dates listed below to be feasible but rather generous.

We are available to discuss by teleconference, if needed.

Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR and PMC studies/trials description to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial.
Final PMR designation numbers will be assigned later.

NDA #	206256
Product Name:	BELEODAQ (belinostat) for injection
PMR Description:	Establish the optimal safe dose of belinostat in combination with the cyclophosphamide/vincristine/doxorubicin/prednisone (CHOP) regimen. Perform a phase 1 dose finding trial of belinostat plus CHOP for the treatment of patients with peripheral T-cell lymphoma (PTCL). Enroll a sufficient number of patients to characterize the safety of the combination of belinostat in combination with the CHOP regimen. Submit a complete study report with all supporting datasets.

PMR Schedule Milestones:	Final Protocol Submission:	Completed
	Trial Completion:	December 2014
	Final Report Submission:	December 2015

NDA #	206256
Product Name:	BELEODAQ (belinostat) for injection
PMR Description:	Characterize the comparative efficacy and safety of Beleodaq when used in combination with a treatment regimen such as CHOP, versus pralatrexate plus CHOP, versus CHOP alone, for the initial therapy of patients with PTCL. Perform a confirmatory, prospective randomized (1:1:1) trial of previously untreated patients with PTCL, with progression free survival (PFS) as the primary efficacy endpoint. Enroll a sufficient number of patients to characterize the efficacy and safety of each drug added to CHOP, versus CHOP alone. The PFS endpoint should be determined by a blinded independent review committee. PFS analysis should be performed when the trial has experienced the planned number of events necessary for trial completion. Using the same data cutoff date as the PFS analysis, perform an interim analysis of overall survival. Submit a complete study report with all supporting datasets.

PMR Schedule Milestones:	Preliminary Protocol Submission:	July 2014
	Final Protocol Submission:	December 2015
	Accrual of 25% of Subjects:	April 2017
	Accrual of 50% of Subjects:	April 2018
	Accrual of 75% of Subjects:	April 2019
	Trial Completion:	January 2020
	Final Report Submission:	January 2021

Some things you can do to expedite this process:

1. For labeling and PMR/PMCs, reply to our drafts ASAP, and be sure to send the RPM a courtesy copy by email. Reply with your edits in a WORD document that you submit by email as well as to the document room. Use track changes to show YOUR edits. ACCEPT all of the track changes edits of ours with which you agree. You may provide annotation within the PI or, if extensive, in a separate document.

2. Assuming, and following a favorable action, you will then be submitting protocols intended to address the objectives of the PMRs agreed upon. We ask the following:

a. For any new studies, it is necessary to submit the protocol for DHP review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol and DHP has advised you that the protocol is judged acceptable to address the PMR/PMC. A fulfillment decision requires review.

b. Send the RPM an email courtesy copy of the draft versions, in WORD, as well as to the EDR officially. Again, for iterations, accept track changes sent to you that you agree with, and only return to us YOUR edits in track changes.

c. It is critical that you advise, prominently, both with the email and cover letter to the EDR that the protocol you are sending is to address a SPECIFIC POST MARKETING REQUIREMENT OR COMMITMENT (WITH THE PMR NUMBER). This helps the document room and us code the submission properly. All protocol submissions are made to the IND.

Thank you,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(301) 796-5357 (phone)
(301) 796-9849 (fax)

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/s/

JESSICA L BOEHMER
05/14/2014

Boehmer, Jessica

From:	Boehmer, Jessica
Sent:	Wednesday, May 14, 2014 2:12 PM
To:	Anil Hiteshi (anil.hiteshi@sppirx.com)
Cc:	Boehmer, Jessica
Subject:	RESPONSE REQUIRED: Clinical Pharmacology Information Request: NDA 206256 - response due today
Importance:	High

Dear Mr. Hiteshi,

In reference to your NDA for Beleodaq (belinostat) for Injection, NDA 206256, submitted December 8, 2014 and received December 9, 2014, the reviewers have identified the following Clinical Pharmacology Information Request. Please respond via email by the date indicated.

Clinical Pharmacology Information Request:

Please provide the final protocols for the ongoing mass balance and hepatic impairment trials. Please also provide details regarding the status of the trials including current enrollment and projected trial completion dates.

Please provide this information by COB today.

Please respond to this new Information Request via email by **close-of-business today, May 14, 2014**. You will also need to officially submit this information to your NDA.

Please confirm receipt of this email.

Thank you,

Jessica

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/s/

JESSICA L BOEHMER
05/14/2014

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Tuesday, May 13, 2014 4:47 PM
To: Anil Hiteshi (anil.hiteshi@sppirx.com)
Cc: Boehmer, Jessica
Subject: FDA Proposed Revisions to PI & Carton/Container Comments: NDA 206256 - Beleodaq (belinostat) for Injection - response due May 16
Attachments: FDA_Proposed_Edits_NDA_206256_PI_13May2014.doc

Importance: High

Dear Anil,

Please see attached revised draft of the **PI for NDA 206256 for Beleodaq (belinostat) for Injection.**

Please review the Agency's changes/comments and do the following to the same draft:

- - Accept any changes that you agree with
- - Edit over the ones that you do not agree with **(do not reject any changes that the FDA proposed)**
- - Make revisions requested in the comments section

After you have made the changes, please send me the revised **tracked changes** document (Word version). Do not officially submit the revised PI at this time.

Please provide a revised PI to me by close of business on **Friday, May 16, 2014.**

These are the Agency's preliminary revisions, and there may be additional proposed revisions during continued labeling discussions. FDA comments on the proposed Patient Labeling will be forthcoming.

Please also reference your amendment dated May 2, 2014, containing revised **Carton and Container Labeling** for **NDA 206256 for Beleodaq (belinostat) for Injection.**

Container Label
1). The statement "Further dilution with Sodium Chloride Injection, 0.9% is required" appears to blend in with other information on the side panel. We recommend making this statement more prominent by bolding and placing on the principal display panel if space permits. This can be achieved by decreasing the prominence of the "Rx only" statement by moving this statement to the side panel and making it less prominent.

2) The "Rx only" statement still appears more prominent than the established name of the product and creates clutter. Therefore, decrease the prominence of that statement by reducing its size and possibly moving to the side panel.

Carton Labeling
1). Increase the prominence of the statement "Further dilution with Sodium Chloride Injection, 0.9% is required" by increasing font size, bolding, and placing on the other side panel (e.g., on the side panel that contains the usual dosing statement).

Please provide revised carton and container labels by close of business on **Friday, May 16, 2014.**

Thank you,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(301) 796-5357 (phone)
(301) 796-9849 (fax)

18 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JESSICA L BOEHMER
05/13/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 070789

MEETING MINUTES

Spectrum Pharmaceuticals, Inc.
Attention: Anil K. Hiteshi, RAC
Vice President, Global Regulatory Affairs
157 Technology Drive
Irvine, CA 92618

Dear Mr. Hiteshi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Beleodaq™ (belinostat) for Injection.

We also refer to the meeting between representatives of your firm and the FDA on April 11, 2014. The purpose of the meeting was to discuss the post-marketing commitment study for Beleodaq.

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

If you have any questions, call Jessica Boehmer, Senior Regulatory Project Manager at (301) 796-5357.

Sincerely,

{See appended electronic signature page}

Virginia Kwitkowski, MS, RN, ACNP-BC
Lead Clinical Analyst, Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A
Meeting Category: Other: Postmarketing Study Discussion

Meeting Date and Time: April 11, 2014, 2:30 PM – 3:30 PM ET
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1421
Silver Spring, Maryland 20903

Application Number: IND 070789
Product Name: Beleodaq™ (belinostat) for Injection
Indication: Treatment of Patients with Relapsed or Refractory Periperal T-Cell Lymphoma
Sponsor/Applicant Name: Spectrum Pharmaceuticals, Inc.

Meeting Chair: Virginia Kwitkowski
Meeting Recorder: Jessica Boehmer

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)
Tamy Kim, PharmD, Associate Directory for Regulatory Affairs

Division of Hematology Products (DHP)
Ann Farrell, MD, Director
Robert Kane, MD, Deputy Director for Safety
Virginia Kwitkowski, MS, RN, ACNP-BC, Lead Clinical Analyst, Clinical Team Leader
Hyon-Zu Lee, PharmD, Clinical Reviewer
Toni-Ann Cox, BA, LPN, Regulatory Project Manager
LCDR Lin Tzeng, BSN, MS (HSM), Regulatory Project Manager
Rachel McMullen, MPH, Regulatory Project Manager
Jessica Boehmer, MBA, Senior Regulatory Project Manager

Office of Biostatistics (OB), Division of Biometrics (DB)
Erik Bloomquist, PhD, Statistical Reviewer

Office of Chief Counsel
Deborah Chasan- Sloan, Attorney

SPONSOR ATTENDEES

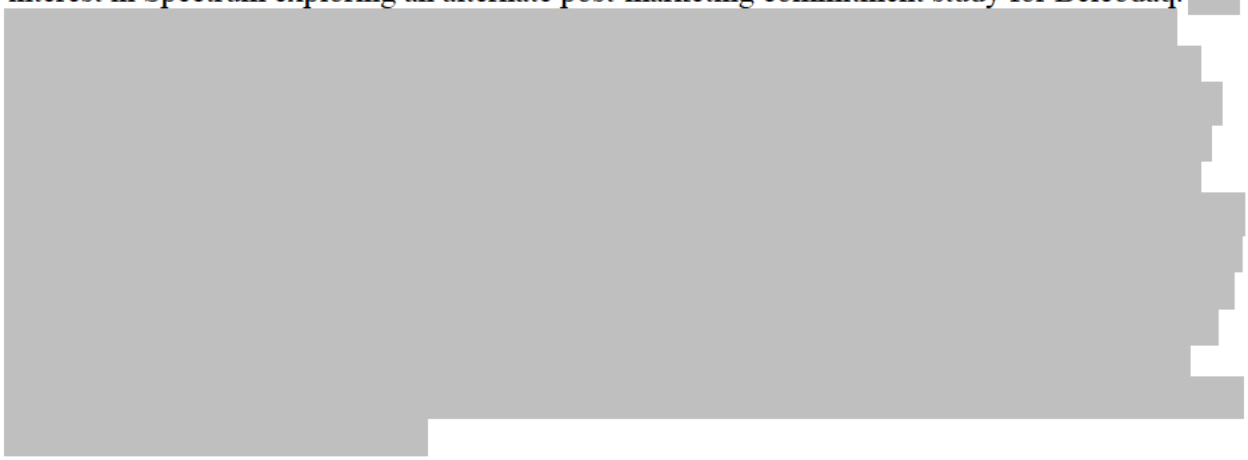
Spectrum Pharmaceuticals, Inc.
Rajesh C. Shrotriya, MD, Chairman, Chief Executive Officer, & President
Lee F. Allen, MD, PhD, Chief Medical Officer
Gajanan Bhat, PhD, Executive Director, Biostatistics, Data Management & Medical Writing
Guru Reddy, PhD, Vice President, Preclinical R&D
Mi Rim Choi, MD, Director, Clinical Research
Anil K. Hiteshi, RAC, Vice President, Global Regulatory Affairs

1.0 BACKGROUND

On May 28, 2008, belinostat was granted Fast Track designation for relapsed or refractory PTCL after at least one prior systemic therapy. Under the Special Protocol Assessment (SPA) process, the FDA agreed on September 4, 2008 that the design and planned analyses of the PXD101-CLN-19 (CLN-19) study, with a primary efficacy endpoint of objective response rate, were adequate to address the objectives necessary to support a regulatory submission. On September 3, 2009, belinostat was granted Orphan Drug designation for the treatment of patients with PTCL.

Spectrum submitted NDA 206256 in December 2013 for Beleodaq, a histone deacetylase (HDAC) inhibitor, for the treatment of patients with relapsed or refractory PTCL. The CLN-19 study that was previously agreed to with FDA under SPA, "A Multicenter, Open-Label Trial of Belinostat in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma," served as the primary basis of safety and efficacy for this NDA. In the NDA submission, Spectrum provided the rationale for a Priority Review designation for the Beleodaq NDA, which was granted by the Agency in the February 5, 2014 Filing Communication Letter.

At the request of FDA, Spectrum presented an overview of NDA 206256 at an Application Orientation Presentation on January 6, 2014. During this meeting, the Agency expressed their interest in Spectrum exploring an alternate post-marketing commitment study for Beleodaq. (b) (4)



2. DISCUSSION

2.1. Clinical Questions

Question 1:

(b) (4)

does the Agency agree that Spectrum should move forward with a postmarketing commitment study that includes both Beleodaq and Folotyn?

FDA Response to Question 1:

Yes. We agree that Spectrum should move forward with a post-marketing confirmatory trial that includes belinostat and pralatrexate.

Discussion:

No discussion occurred.

Question 2:

Based on the discussion summarized above in Question 1, Spectrum proposes a design for a Phase 3 confirmatory study as the alternate post-marketing commitment study. This trial would serve to satisfy the requirement to conduct a confirmatory study to demonstrate the clinical benefit of Beleodaq and Folotyn.

Does the Agency agree?

FDA Response to Question 2:

Trial design option 1, "A Phase 3, Randomized, Open-Label, Study Comparing Efficacy and Safety of Beleodaq-CHOP or Folotyn-CHOP versus CHOP Regimen Alone in Newly Diagnosed Patients with Previously Untreated Peripheral T-Cell Lymphoma" is preferred as the alternative confirmatory trial.

Specific comments on the selected trial will be provided once the protocol has been submitted to the Agency.

Discussion:

The Agency and the Sponsor discussed various proposals for the PTCL and CTCL PMRs for Folotyn.

The Agency suggests that the sponsor submit data and information supporting their proposals presented at the meeting in a Type C WRO request. The Agency will meet internally to discuss and respond.

3.0 PREA REQUIREMENTS

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

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

The Sponsor will submit data and information supporting their proposals presented at the meeting in a Type C WRO request.

6.0 ATTACHMENTS AND HANDOUTS

Please see attached slides.

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/s/

VIRGINIA E KWITKOWSKI
05/01/2014

Boehmer, Jessica

From:	Boehmer, Jessica
Sent:	Wednesday, April 16, 2014 4:52 PM
To:	Anil Hiteshi (anil.hiteshi@sppirx.com)
Cc:	Boehmer, Jessica
Subject:	RESPONSE REQUIRED: Information Request: NDA 206256 due May 2
Importance:	High

Dear Mr. Hiteshi,

In reference to your NDA for Beleodaq (belinostat) for Injection, NDA 206256, submitted December 8, 2014 and received December 9, 2014, the reviewers have identified the following Information Request. Please respond via email by the date indicated.

Information Request:

Carton and Container Labels:

1. Revise the proprietary name to state "Beleodaq" since this name was conditionally approved on March 4, 2014. We recommend capitalizing only the first letter in the proprietary name because words written in all-capital letters are less legible than words written in mixed case letters.

2. Revise the product strength statement to "500 mg per vial" which is the customary format for injectable products that require reconstitution.

3. Revise the route of administration statement to "For Intravenous Infusion Only" to help ensure the correct use of the drug and place this information immediately underneath the strength of the product to help with readability of this important information.

4. The vial is meant as a single dose product, therefore revise the single use statement to read "Single-Use Vial. Discard Unused Portion". Place this information under the route of administration to help with readability.

5. The location of the "Rx only" appears more prominent than the established name of the product and creates clutter. Therefore, de-bold, reduce the size of the statement and relocate away from the other important information on the principal display panel2.

6. Delete the word (b) (4) from the principal display panel (PDP) as this information does not carry any significant information and clutters PDP.

7. Add the statement "Further dilution with Sodium Chloride Injection, 0.9 % is required" to the side panel of the label and labeling if space permits.

Please respond to this new Information Request via email by **Friday, May 2, 2014**. You will also need to officially submit this information to your NDA.

Please confirm receipt of this email.

Thank you,

Jessica

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/s/

JESSICA L BOEHMER
04/16/2014

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Tuesday, April 15, 2014 9:47 AM
To: Anil Hiteshi
Cc: Boehmer, Jessica
Subject: RESPONSE NEEDED: FDA Clinical Pharmacology Information Request: NDA 206256: due April 17

Importance: High

Dear Mr. Hiteshi,

In reference to your NDA for Beleodaq (belinostat) for Injection, NDA 206256, submitted December 8, 2014 and received December 9, 2014, the reviewers have identified the following Clinical Information Request. Please respond via email by the date indicated.

Clinical Pharmacology Information Request:

We have reviewed your in vitro drug metabolism studies (1981-035 & 2525-009), in vitro drug-drug interaction study (solvo-topotarget-01), and the cited literature reference (Want et al, 2013) to determine the percentage contributions of each P450 (CYP3A4, CYP3D6, & CP2C9) and UGT1A1 enzyme in the biotransformation of Beleodaq. However, none of the submitted study reports or written summaries provides definitive information regarding the exact contributions of each of the cited enzymes in the biotransformation of Beleodaq. Please submit additional study reports or documents that characterize the contributions of each metabolizing enzymes. If you don't have the study reports, please provide a plan on how you intend to address the lack of this important information.

Please respond to this new Clinical Pharmacology Information Request via email by **4:00 PM Thursday, April 17, 2014**. You will also need to officially submit this information to your NDA.

Please confirm receipt of this email.

Thank you,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(301) 796-5357 (phone)
(301) 796-9849 (fax)

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/s/

JESSICA L BOEHMER
04/15/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206256

INFORMATION REQUEST

Spectrum Pharmaceuticals, Inc.
Attention: Anil K. Hiteshi, RAC
Vice President, Global Regulatory Affairs
157 Technology Drive
Irvine, CA 92618

Dear Mr. Hiteshi:

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

We also refer to your original NDA submission.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response by April 9, 2014, in order to continue our evaluation of your NDA.

1. Please provide the references used that identify the doses at which (b) (4) impurities present in belinostat drug substance are mutagenic in nonclinical test systems. Also provide a detailed description of the calculations used that justify their proposed release specifications.

If you have any questions, call Teicher Agosto, Regulatory Project Manager, at (240) 402-3777.

Sincerely,

{See appended electronic signature page}

Ali H. Al Hakim, PhD
Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

ALI H AL HAKIM
04/01/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206256

MID-CYCLE COMMUNICATION

Spectrum Pharmaceuticals, Inc.
Attention: Anil K. Hiteshi, RAC
Vice President, Global Regulatory Affairs
157 Technology Drive
Irvine, CA 92618

Dear Mr. Hiteshi:

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

We also refer to the teleconference between representatives of your firm and the FDA on March 17, 2014. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Jessica Boehmer, Senior Regulatory Project Manager at (301) 796-5357.

Sincerely,

{See appended electronic signature page}

Virginia Kwitkowski, MS, RN, ACNP-BC
Lead Clinical Analyst
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: March 17, 2014, 1:00 PM – 2:00 PM ET

Application Number: NDA 206256
Product Name: Beleodaq™ (belinostat) for Injection
Indication: Treatment of Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma
Applicant Name: Spectrum Pharmaceuticals, Inc.

Meeting Chair: Virginia Kwitkowski
Meeting Recorder: Jessica Boehmer

FDA ATTENDEES

Division of Hematology Products (DHP)
Edvardas Kaminskas, MD, Deputy Director
Virginia Kwitkowski, MS, RN, ACNP-BC, Lead Clinical Analyst, Clinical Team Leader
Hyon-Zu Lee, PharmD, Clinical Reviewer
Qin Ryan, MD, MPH, Safety Medical Officer
Amy Chi, MSN, Regulatory Project Manager
Jessica Boehmer, MBA, Senior Regulatory Project Manager

Office of Biostatistics (OB), Division of Biometrics (DB)
Erik Bloomquist, PhD, Statistical Reviewer

Office of New Drug Quality Assessment (ONDQA)
Janice Brown, MS, CMC Lead
Xiao-Hong Chen, PhD, Reviewer

Division of Hematology Oncology Toxicology (DHOT)
Haleh Saber, PhD, Supervisory Pharmacologist
Stacey Ricci, M Eng, ScD, Reviewer
Pedro Del Valle, PhD, Reviewer

Office of Clinical Pharmacology (OCP)
Bahru Habtemariam, PharmD, Reviewer

Office of Surveillance and Epidemiology (OSE), Division of Risk Management (DRISK)
Carolyn Yancey, MD, Reviewer

Office of Surveillance and Epidemiology (OSE), Office of Prescription Drug Promotion (OPDP)
James Dvorsky, PhD, Reviewer

EASTERN RESEARCH GROUP ATTENDEES

(b) (6)

APPLICANT ATTENDEES

Spectrum Pharmaceuticals, Inc.
Rajesh C. Shrotriya, MD, Chairman, Chief Executive Officer, and President
Lee F. Allen, MD, PhD, Chief Medical Officer
Gajanan Bhat, PhD, Executive Director, Biostatistics, Data Management and Medical Writing
Guru Reddy, PhD, Vice President, Preclinical R&D
Pramod K. Gupta, PhD, Vice President, Pharmaceutical Operations
Mi Rim Choi, MD, Director, Clinical Research
Anil K. Hiteshi, RAC, Vice President, Global Regulatory Affairs

Topotarget
Anne Sillemann, M.Sc., Pharm, Head of Global Regulatory Affairs
Karsten Witt, MD, Board Member

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

CMC particulate issue

3.0 INFORMATION REQUESTS

Sent by CMC:

The high level of particulates observed in the Belinostat dilution admixture in 0.9% Sodium Chloride Injection in either (b) (4) bags raises concerns regarding the safety of the drug being administered intravenously to patients. Although a 0.22 μm in-line filter

was able to reduce the particulate levels to meeting the USP<788> specification for the large volume parenterals, you should explore whether alternative infusion sets and/or diluents that can be used are compatible to the Belinostat dilution admixture. It is recommended that you conduct study using both the drug product and the drug product formulation without the active ingredient to determine whether the particulates were caused by the excipients or the drug substance and determine the nature of the particulates.

Spectrum stated that they intend to respond to the CMC information request by March 28, 2014 and to communicate with the CMC FDA team with regard to any delays expected.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There is currently no need for a REMS.

5.0 ADVISORY COMMITTEE MEETING

There are no plans at this time for an AC meeting

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

We anticipate we will begin labeling discussions by May 13, 2014.

The Late-Cycle Meeting is scheduled to take place June 4, 2014.

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/s/

VIRGINIA E KWITKOWSKI
03/19/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206256

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Spectrum Pharmaceuticals, Inc.
157 Technology Drive
Irvine, CA 92618

Attention: Mr. Anil K. Hiteshi, RAC
Vice President, Global Regulatory Affairs

Dear Mr. Hiteshi:

Please refer to your New Drug Application (NDA) dated December 8, 2013, received December 9, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Belinostat Powder for Injection, 500 mg per vial.

We also refer to your February 25, 2014, correspondence, received February 25, 2014, requesting review of your proposed proprietary name, Beleodaq. We have completed our review of the proposed proprietary name, Beleodaq, and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your February 25, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sonny Saini, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0532. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Jessica Boehmer at (301) 796-5357.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, PharmD., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
03/16/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206256

INFORMATION REQUEST

Spectrum Pharmaceuticals, Inc.
Attention: Anil K. Hiteshi, RAC
Vice President, Global Regulatory Affairs
157 Technology Drive
Irvine, CA 92618

Dear Mr. Hiteshi:

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

We also refer to your original NDA submission.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a written response by March 28, 2014, in order to continue our evaluation of your NDA.

1. The high level of particulates observed in the Belinostat dilution admixture in 0.9% Sodium Chloride Injection in [redacted] (b) (4) bags raises concerns regarding the safety of the drug being administered intravenously to patients. Although a 0.22 µm in-line filter was able to reduce the particulate levels to meeting the USP<788> specification for the large volume parenterals, you should explore whether alternative infusion sets and/or diluents that can be used are compatible to the Belinostat dilution admixture. It is recommended that you conduct study using both the drug product and the drug product formulation without the active ingredient to determine whether the particulates were caused by the excipients or the drug substance and determine the nature of the particulates.

2. The proposed drug product specification limit for [redacted] (b) (4) is too broad based on the batch release and stability data. There is insignificant change of [redacted] (b) (4) after 36 months storage under the long term conditions. Tighten the acceptance limit for [redacted] (b) (4) based on batch analysis data or provide justification to demonstrate that high level of [redacted] (b) (4) does not impact stability (degradation) of Belinostat drug substance.

3. Revise the post-approval long term stability (25°C/60%RH) testing time points for the annual drug product stability program as follows: 0, 3, 6, 9, 12, 18, 24, 36, 48, and 60 months.

4. Reference is made to (1) the proposed product labeling which specifies that the drug product is reconstituted with 0.9 mL WFI and stored for up to (b) (4) hours at room temperature, and then further diluted in 250 mL 0.9% NaCl and stored for up to (b) (4) hours at room temperature, and (2) the microbiological challenge study (b) (4) Report No. 734025) which concludes that the admixed product may be stored for up to (b) (4) hours. The following comment is provided in response to the proposed labeling which specifies a (b) (4)-hour holding time (at room temperature) between drug product reconstitution/admixture and patient administration:

   a. Microbiological data should be provided in the NDA to demonstrate that the reconstituted product solution will not support microbial growth during the proposed (b) (4)-hour (room temperature) storage period. Please provide a risk assessment summarizing studies that show adventitious microbial contamination does not grow under the storage conditions. Reference is made to Guidance for Industry: ICH Q8 Pharmaceutical Development, Section II.E and Guidance for Industry: ICH Q1A(R2) Stability Testing of New Drug Substances and Products, Section 2.2.7.

   b. Generally, "no growth" is interpreted as not more than a 0.5 $\log_{10}$ increase from the initial count; however other evidence of growth may be significant. The test should be run at the label's recommended storage conditions, be conducted for 2 to 3-times the label's recommended storage period, and use the label-recommended fluids inoculated with low numbers (≤100 CFU/mL) of challenge microbes. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections. In lieu of these data, the product labeling should recommend that the post-constitution storage period is not more than (b) (4) hours at room temperature.

Please note that there are outstanding deficiencies for the referenced Type II DMF 26926 to be addressed by the DMF holder.

If you have any questions, please contact Teicher Agosto, Regulatory Project Manager, at (240) 402-3777.

Sincerely,

{See appended electronic signature page}

Ali H. Al Hakim, PhD
Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

ALI H AL HAKIM
03/14/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206256

MEETING REQUEST WITHDRAWN

Spectrum Pharmaceuticals, Inc.
Attention: Anil K. Hiteshi, RAC
Vice President, Global Regulatory Affairs
157 Technology Drive
Irvine, CA 92618

Dear Mr. Hiteshi:

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

We also refer to your March 10, 2014 communication requesting withdrawal of your March 6, 2014 meeting request because, as requested by the Agency, Spectrum has re-submitted this meeting request under IND 070789. Your meeting request is hereby withdrawn.

If you have any questions, call me at (301) 796-5357.

Sincerely,

{See appended electronic signature page}

Jessica Boehmer, M.B.A.
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

JESSICA L BOEHMER
03/12/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206256

METHODS VALIDATION
MATERIALS RECEIVED

Spectrum Pharmaceuticals, Inc.
Attention: Anil K. Hiteshi, RAC, Vice President, Global Regulatory Affairs
157 Technology Drive
Irvine, CA 92618

Dear Anil K. Hiteshi:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Beleodaq (Belinostat) for injection, 500 mg/vial and to our January 27, 2014, letter requesting sample materials for methods validation testing.

We acknowledge receipt on February 25, 2014, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
02/26/2014

Boehmer, Jessica

From:	Boehmer, Jessica
Sent:	Wednesday, February 26, 2014 9:49 AM
To:	'Anil Hiteshi'
Cc:	Boehmer, Jessica
Subject:	RESPONSE NEEDED: FDA Clinical Information Request: NDA 206256: due March 3
Importance:	High

Dear Mr. Hiteshi,

In reference to your NDA for Beleodaq (belinostat) for Injection, NDA 206256, submitted December 8, 2014 and received December 9, 2014, the reviewers have identified the following Clinical Information Request. Please respond via email by the date indicated.

Clinical Information Request:

There were 22 reported deaths in the CLN-19 trial. However, from the dataset there were 17 more patients that were censored and had a survival date within 30 days of the last dose of belinostat. Please provide the cause of deaths of the 17 patients.

We would also like to follow-up regarding the following issue and Information Requests included in the February 5, 2014 Filing Letter:

Clinical:
We remind you of our conversation during your Applicant Orientation Presentation on January 6, 2014, where we requested that you submit a meeting request to discuss an alternative confirmatory trial design (b) (4) .
We are reserving our decision whether to present this application at an Advisory Committee meeting until this meeting has occurred.

Clinical Information Request

1. Provide the number of investigators in the CLN-19 trial who are sponsor employees (including both full-time and part-time employees).

Statistical Information Request

2. Provide the programs used to calculate the median duration of response and time to response, as shown in the last part of Section 14 of the labeling.

Please respond to this new Clinical Information Request and the Clinical Issue and Clinical and Statistical Information Requests included in the Filing Letter via email by **Tuesday, March 3, 2014**. You will also need to officially submit this information to your NDA.

Please confirm receipt of this email.

Thank you,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(301) 796-5357 (phone)
(301) 796-9849 (fax)

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/s/

JESSICA L BOEHMER
02/26/2014

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Wednesday, February 26, 2014 7:01 AM
To: Anil Hiteshi
Cc: Boehmer, Jessica
Subject: RESPONSE NEEDED: FDA Clinical Pharmacology Information Request: NDA 206256: due Feb 26

Importance: High

Dear Mr. Hiteshi,

In reference to your NDA for Beleodaq (belinostat) for Injection, NDA 206256, submitted December 8, 2014 and received December 9, 2014, the reviewers have identified the following Clinical Pharmacology Information Request. Please respond via email by the date indicated.

Clinical Pharmacology Information Request:

The AUC estimate for the final model was not included in "109.TAB". Please update and send "109.TAB" within 1-2 hours.

Please respond to this Information Request via email by **today, February 26, 2014**. You will also need to officially submit this information to your NDA.

Please confirm receipt of this email.

Thank you,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(301) 796-5357 (phone)
(301) 796-9849 (fax)

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/s/

JESSICA L BOEHMER
02/26/2014

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Friday, February 21, 2014 12:47 PM
To: Anil Hiteshi (anil.hiteshi@sppirx.com)
Cc: Boehmer, Jessica
Subject: RESPONSE NEEDED: FDA Clinical Pharmacology Information Request: NDA 206256: due Feb 24

Importance: High

Dear Mr. Hiteshi,

In reference to your NDA for Beleodaq (belinostat) for Injection, NDA 206256, submitted December 8, 2014 and received December 9, 2014, the reviewers have identified the following Clinical Pharmacology Information Request. Please respond via email by the date indicated.

Clinical Pharmacology Information Request:

We were unable to successfully run your final population PK model using the versions of datasets submitted with the NDA. Please submit the following items:

1. Using final population PK parameter estimates, please provide AUC estimates for all patients that took part in the population PK analysis. This dataset should include unique patient ID, study ID, Dose, and basic patient covariates. The patient ID should be identical to the patient IDs in the safety efficacy datasets for successful merging. You may submit this dataset in *xpt format.
2. Submit the exact copy of the population PK dataset that was used to run the final population PK model. This dataset maybe submitted *csv format.
3. Also submit NONMEM control stream codes for the base and final model. The control stream should be in a text format.

Please respond to this Information Request via email by **4:00 PM** on **Monday, February 24, 2014**. You will also need to officially submit this information to your NDA.

Please confirm receipt of this email.

Thank you,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(301) 796-5357 (phone)
(301) 796-9849 (fax)

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/s/

JESSICA L BOEHMER
02/21/2014

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Thursday, February 20, 2014 1:46 PM
To: Anil Hiteshi (anil.hiteshi@sppirx.com)
Cc: Boehmer, Jessica
Subject: RESPONSE NEEDED: FDA Nonclinical Information Request: NDA 206256: due Feb 24

Importance: High

Dear Mr. Hiteshi,

In reference to your NDA for Beleodaq (belinostat) for Injection, NDA 206256, submitted December 8, 2014 and received December 9, 2014, the reviewers have identified the following Nonclinical Information Request. Please respond via email by the date indicated.

Nonclinical Information Request:

In order to expedite the nonclinical data review, please provide the pathology reports for studies 2525-001 "PXD101 : Cyclic Intravenous Dosing Study in the Rat (8 Cycles over 24 Weeks)" and 2525-013 "PXD101 : Cyclic Intravenous Dosing Study in the Dog (8 Cycles over 24 Weeks)". Pathology reports should clearly indicate the method of grading microscopic findings and include the intergroup comparison with the severity grading of each finding.

Please respond to this Information Request via email by **4:00 PM** on **Tuesday, February 24, 2014**. You will also need to officially submit this information to your NDA.

Please confirm receipt of this email.

Thank you,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(301) 796-5357 (phone)
(301) 796-9849 (fax)

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/s/

JESSICA L BOEHMER
02/20/2014

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Tuesday, February 11, 2014 11:35 AM
To: Anil Hiteshi (anil.hiteshi@sppirx.com)
Cc: Boehmer, Jessica
Subject: RESPONSE NEEDED: FDA Information Request: NDA 206256: due Feb 14

Importance: High

Dear Mr. Hiteshi,

In reference to your NDA for Beleodaq (belinostat) for Injection, NDA 206256, submitted December 8, 2014 and received December 9, 2014, the reviewers have identified the following Information Request. Please respond via email by the date indicated.

Information Request:

Please provide clarification of the response assessment by IRC on the following 3 patients:

1. According to Listing 16.2.6.1 (Response evaluation by IRC), patient 244-003 had PRs (assessments 1-10), CR on May 22, 2012 (assessment 11), PD on August 10, 2012 (assessment 12) and this patient was declared as CR. According to Listing 16.2.6.3 (Target lesions by IRC), the measurements of the nasopharynx lesion at baseline was 30mm x21mm. The measurement at assessment 10 was 33mm x18mm, UE x UE at assessment 11 and 32mm x22mm at assessment 12. The greatest transverse diameter never decreased to ≤ 15 mm required for a CR. Please provide clarification how this patient was assessed as a CR.

2. Patient 534-001 was assessed to have a CR on May 12 (assessment 2) and June 23, 2010 (assessment 3) in Listing 16.2.6.1. According to Listing 16.2.6.3, the measurements of abdominal nodes were 25mm x 9mm (assessment 2) and 24mm x 7mm (assessment 3). Please provide clarification how this patient was assessed as a CR.

3. Patient 800-001 was assessed to have a PR on February 6, 2011 (assessment 1) in Listing 16.2.6.1. According to Listing 16.2.6.3, the % change from baseline for the lesions were -20.0% (reviewer 1) and -30.3% (reviewer 2) and did not decrease ≥ 50% required for a PR. Please provide clarification how this patient was assessed as a PR.

Also, provide the variable(s) used to assess median follow-up time in time to event endpoints (i.e., TTP, PFS, OS).

Please respond to this Information Request via email by **4:00 PM on Friday, February 14, 2014**. You will also need to officially submit this information to your NDA.

Please confirm receipt of this email.

Thank you,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(301) 796-5357 (phone)
(301) 796-9849 (fax)

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/s/

JESSICA L BOEHMER
02/11/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206256

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

Spectrum Pharmaceuticals, Inc.
Attention: Anil K. Hiteshi, R.A.C.
Vice President, Global Regulatory Affairs
157 Technology Drive
Irvine, CA 92618

Dear Mr. Hiteshi:

Please refer to your New Drug Application (NDA) dated December 8, 2013, received December 9, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Beleodaq™ (belinostat) for Injection.

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 **Priority**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm. Therefore, the user fee goal date is August 9, 2014.

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 requirement/commitment requests by May 13, 2014. In addition, the planned date for our internal mid-cycle review meeting is March 7, 2014. We are not currently planning to hold an advisory committee meeting to discuss this application.

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

Clinical:

We remind you of our conversation during your Applicant Orientation Presentation on January 6, 2014, where we requested that you submit a meeting request to discuss an alternative confirmatory trial design (b) (4) We are reserving our decision whether to present this application at an Advisory Committee meeting until this meeting has occurred.

We are providing the above comment to give you preliminary notice of a potential review issue. 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. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

Clinical Information Request

1. Provide the number of investigators in the CLN-19 trial who are sponsor employees (including both full-time and part-time employees).

Statistical Information Request

2. Provide the programs used to calculate the median duration of response and time to response, as shown in the last part of Section 14 of the labeling.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. Insert a horizontal line to separate the Highlights from the Table of Contents. Also, insert a horizontal line to separate the TOC from the FPI.
2. In Adverse Reactions in Highlights the following verbatim bolded statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**". The manufacturer's website address should not be included.
3. In the Table of Contents, indent the subsection headings.
4. Correct the statement at the end of the Table of Contents. It should read: "*Sections or subsections omitted from the full prescribing information are not listed."

5. Correct the cross-references in the FPI so that the section (not subsection) heading is followed by the numerical identifier. For example: "[*see Warnings and Precautions (5.2)*]"
6. FDA-approved patient labeling (e.g., Patient Information) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). Patient labeling must appear at the end of the PI.

We request that you resubmit labeling that addresses these issues by February 14, 2014. The resubmitted labeling will be used for further labeling discussions.

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

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Jessica Boehmer, Regulatory Project Manager, at (301) 796-5357.

Sincerely,

{See appended electronic signature page}

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

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/s/

ANN T FARRELL
02/05/2014

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Tuesday, January 28, 2014 1:15 PM
To: Anil Hiteshi (anil.hiteshi@sppirx.com)
Cc: Boehmer, Jessica
Subject: RESPONSE NEEDED: FDA Information Request: NDA 206256: due Feb 4
Attachments: HighlightsofClinicalPharmacology.doc

Importance: High

Dear Mr. Hiteshi,

In reference to your NDA for Beleodaq (belinostat) for Injection, NDA 206256, submitted December 8, 2014 and received December 9, 2014, the reviewers have identified the following Information Request. Please respond via email by the date indicated.

Information Request:

Complete the attached "Highlights of Clinical Pharmacology" table.

Please respond to this Information Request via email by **4:00 PM** on **Tuesday, February 4, 2014**. You will also need to officially submit this information to your NDA.

Please confirm receipt of this email.

Thank you,

Jessica

Jessica Boehmer, MBA
Senior Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(301) 796-5357 (phone)
(301) 796-9849 (fax)

Highlights of Clinical Pharmacology

Therapeutic dose	Include maximum proposed clinical dosing regimen.	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	• Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	• Primary route; percent dose eliminated • Other routes
	Terminal t½	• Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical	Describe worst case scenario and expected fold-change in Cmax and	

Exposure Scenario	AUC. The increase in exposure should be covered by the supra-therapeutic dose.

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/s/

JESSICA L BOEHMER
01/28/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206256

REQUEST FOR METHODS VALIDATION MATERIALS

Spectrum Pharmaceuticals, Inc.
Attention: Anil K. Hiteshi, RAC
Vice President, Global Regulatory Affairs
157 Technology Drive
Irvine, CA 92618
FAX: (949) 788-6708

Dear Anil K. Hiteshi:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Beleodaq (Belinostat) for injection, 500 mg/vial.

We will be performing methods validation studies on Beleodaq (Belinostat) for injection, 500 mg/vial, as described in NDA 206256.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

TM.1211 Identification, Assay and Impurities of Belinostat Drug Substance by HPLC
TM.1611 (b) (4)
(b) (4) PSC Y738 and (b) (4) 2.1236 Identification, Assay and Related Substances by HPLC

Samples and Reference Standards

2 x 100 mg PXD101 reference standard
2 x 1 g PXD101 drug substance
2 x 25 mg (b) (4) resolution standard
2 x 25 mg (b) (4) reference standard
40 vials of Beleodaq (Belinostat) for injection, 500 mg/vial
5 g of L-arginine
1 g (b) (4) reference standard

Equipment

1 (b) (4)
1 (b) (4)
20 (b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (michael.trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
01/27/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206256

NDA ACKNOWLEDGMENT

Spectrum Pharmaceuticals, Inc.
Attention: Anil K. Hiteshi, R.A.C.
Vice President, Global Regulatory Affairs
157 Technology Drive
Irvine, CA 92618

Dear Mr. Hiteshi:

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: Beleodaq (belinostat) for Injection

Date of Application: December 8, 2013

Date of Receipt: December 9, 2013

Our Reference Number: NDA 206256

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 February 7, 2014, in accordance with 21 CFR 314.101(a).

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

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

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

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

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

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.
If you have any questions, call me at (301) 796-5357.

Sincerely,

{See appended electronic signature page}

Jessica Boehmer, M.B.A.
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

JESSICA L BOEHMER
01/09/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 070789

MEETING MINUTES

Spectrum Pharmaceuticals, Inc.
Attention: Anil K. Hiteshi, R.A.C.
Vice President, Global Regulatory Affairs
157 Technology Drive
Irvine, CA 92618

Dear Mr. Hiteshi:

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

We also refer to the meeting between representatives of your firm and the FDA on May 29, 2013. The purpose of the meeting was to discuss the proposed structure and content of the nonclinical, clinical, and CMC sections in the NDA.

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

If you have any questions, call Jessica Boehmer, Regulatory Project Manager at (301) 796-5357.

Sincerely,

{See appended electronic signature page}

Virginia Kwitkowski, M.S., R.N., A.C.N.P.-B.C.
Lead Clinical Analyst
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: May 29, 2013, 3:00 PM – 4:00 PM, ET
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Application Number: IND 070789
Product Name: Belinostat for Injection
Indication: Belinostat is indicated for the treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL) (b) (4)

Sponsor/Applicant Name: Spectrum Pharmaceuticals, Inc.

Meeting Chair: Virginia Kwitkowski
Meeting Recorder: Jessica Boehmer

FDA ATTENDEES

Division of Hematology Products (DHP)
Edvardas Kaminskas, M.D., Deputy Director
Virginia Kwitkowski, M.S., R.N., A.C.N.P.-B.C., Clinical Team Leader
Hyon-Zu Lee, Pharm.D., Clinical Reviewer
Adam George, Pham.D., Clinical Reviewer
Jessica Boehmer, M.B.A., Regulatory Project Manager

Office of Hematology and Oncology Products (OHOP)
Erik Laughner, M.S., R.A.C., Regulatory Scientist

Office of Biostatistics (OB), Division of Biometrics (DB)
Mark D. Rothmann, Ph.D., Statistical Team Leader
Kyung Y. Lee, Ph.D., Statistical Reviewer

Office of Clinical Pharmacology (OCP)
Julie Bullock, Pharm.D., Clinical Pharmacology Team Leader
Elizabeth Shang, Pharm.D., Clinical Pharmacology Reviewer

Office of Business Informatics (OBI), eData Management Solutions
Douglas Warfield, Ph.D., Interdisciplinary Scientist

EASTERN RESEARCH GROUP ATTENDEES

(b) (6)

SPONSOR ATTENDEES

Spectrum Pharmaceuticals, Inc.
Rajesh C. Shrotriya, M.D., Chairman, Chief Executive Officer, and President
Lee F. Allen, M.D., Ph.D.
Steven Fruchtman, M.D., Senior Vice President, Clinical Research Hematology/Oncology
Shanta Chawla, M.D., Vice President, Clinical Research
Guru Reddy, Ph.D., Vice President, Preclinical Research and Development
Nozar Azarnia, Ph.D., Vice President, Biostatistics and Data Management
Anil K. Hiteshi, R.A.C., Vice President, Global Regulatory Affairs

Topotarget
Ann Sillemann, M.Sc.Pharm., Head of Global Regulatory Affairs
Gisela Schwab, M.D., Board Member

1.0 BACKGROUND

The purpose of this meeting is to discuss the proposed structure and content of the nonclinical and clinical sections in the NDA and to resolve any questions or issues.

Spectrum Pharmaceuticals, Inc. plans to submit a New Drug Application (NDA) in 2013 for belinostat, a histone deacetylase (HDAC) inhibitor, as a single- agent for the treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL) (b) (4) The NDA will be submitted in the electronic common technical document (eCTD) format.

Under the Special Protocol Assessment (SPA) process, the Food and Drug Administration (FDA) agreed on September 4, 2008 that the design and planned analyses of PXD101-CLN-19 (**CLN-19**) adequately addressed the objectives necessary to support an NDA regulatory submission. Data from the **CLN-19** study, entitled, "*A Multicenter, Open-Label Trial of Belinostat in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma*," will serve as the primary basis of safety and efficacy for this NDA. The FDA granted Fast Track Designation to belinostat in the treatment of PTCL on May 28, 2008 and Orphan-drug Designation on September 3, 2009. The Sponsor states, "there continues to be an unmet medical need for treatment options in this patient population as the currently approved drug products have to date not demonstrated clinical benefit such as an improvement in progression-free survival (PFS) or overall survival (OS) in this patient population."

2. DISCUSSION

2.1. Nonclinical

Question 1:

The Sponsor intends to submit a nonclinical dossier consisting of pharmacology, pharmacokinetics (PK), and toxicology as listed in Module 4 of the e-CTD Table of Contents (Appendix 1). The pharmacology data package will consist of *in vitro* studies and studies in a variety of animal models of cancer that demonstrates growth inhibitory activity for belinostat. Safety pharmacology will consist of cardiovascular, respiratory, and central nervous system (CNS) studies. The ADME of belinostat have been studied in a variety of non-radiolabeled and radiolabeled nonclinical studies following single and repeated dosing in rats and dogs, both from specific PK studies as well as from adjunct kinetic studies supporting safety pharmacology and toxicology studies. The general toxicity of belinostat has been evaluated in single-dose and repeat-dose rodent (rat) and non-rodent species (dog). *In vitro* and *in vivo* assays indicate belinostat is genotoxic and thus carcinogenicity and embryofetal toxicology assessment have not been conducted as belinostat is intended to treat patients with advanced cancer. Local tolerance and immunotoxic potential of IV

belinostat was evaluated as part of the general toxicity studies. The Sponsor believes the nonclinical data package is adequate to support the NDA.

Does the Agency agree?

FDA Response to Question 1:

The nonclinical package consisting of the studies listed for Module 4 support the filing of an NDA for belinostat, however, the adequacy of the studies will be a review issue.

Sponsor Response

Sponsor acknowledges the Agency's comments and has no further questions.

Discussion:

No discussion occurred.

2.2. Clinical Pharmacology

Question 2:

The Sponsor intends to submit a clinical pharmacology dossier consisting of PK and pharmacodynamics studies performed in human biomaterials and/or clinical studies as listed in Module 5 of the e-CTD Table of Contents (Appendix 1). *In vitro* studies in human materials were conducted: 1) to identify the metabolism of belinostat by CYP450 isoforms, 2) to evaluate belinostat for potential CYP inhibition and induction, and 3) to evaluate if belinostat is a P-gp substrate in the Caco-2 monolayer efflux assay. The PK profile of IV belinostat and its metabolites were evaluated in several monotherapy or combination therapy clinical studies where plasma samples taken for PK analysis were analyzed. A drug-drug interaction between belinostat and warfarin was evaluated in **CLN-20**. The following two reports for the formal covariate analyses of integrated PK from various clinical studies will be provided in the NDA: 1) Formal PK covariate analyses of noncompartmental exposure/PK estimates from IV belinostat monotherapy or combination therapy studies in advanced malignancies, and 2) PopPK analyses [Draft of the Population Analysis Plan (PAP) provided in Module 5.3.3.5] using sparse PK samples from **CLN-19** to explore exposure-response relationships for measurements of effectiveness and toxicity. Additional PK data from other IV belinostat monotherapy or combination therapy studies (**TT-20**, **CLN-8**, **CLN-15** and **CLN-20**) will be included in the PopPK analyses to provide additional PK data to develop and qualify a robust population PK model for belinostat and its major metabolite, belinostat glucuronide. The ECG raw data from various clinical studies will be integrated to analyze exposure-response in accordance with FDA recommendations [See Module 1.6.3 for minutes of Type C meeting held on 20 July 2011]. The Sponsor believes the Clinical Pharmacology data package is adequate to support the planned NDA submission.

Does the FDA agree?

FDA Response to Question 2:

Yes, assuming you commit to submitting the final report and datasets for CLN-20 within 30 days after filing the NDA application.

Sponsor Response

Sponsor acknowledges the Agency's comments and will plan to submit the final report and datasets for the CLN-20 study within 30 days after filing the NDA.

Discussion:

No discussion occurred at the meeting. Post-meeting comment to Sponsor: The final report and datasets for the CLN-20 study should be submitted to the NDA within 30 days after submission of the NDA.

In principle, your plan of conducting the population PK analysis appears reasonable. We have the following recommendations.

- **Based on your population pharmacokinetic plan, apart from including sparse PK data collected in CLN-19, you propose to include data from TT-20, CLN-8, CLN-15 and CL-20 in the analysis. We recommend you to include data from other relevant PK studies as well for development of the population PK model.**

Sponsor Response

Sponsor acknowledges that the relevant PK studies will be included in the development of the population PK model and has no further questions.

Discussion:

No discussion occurred.

- **To evaluate the impact of liver function on PK of belinostat, you propose to test AST, ALT and total bilirubin (TB) levels as covariates in population PK. We also recommend using NCI-ODWG criteria to classify the patients with into different hepatic impairment categories and evaluate its impact on PK of belinostat. NCI-ODWG criteria is based on TB and AST:**
    - **Normal: TB and AST < upper limit of normal (ULN)**
    - **Mild hepatic impairment (TB > ULN to 1.5 x VLN or AST > ULN)**
    - **Moderate hepatic impairment (TB > 1.5 to 3 x ULN, any AST)**
    - **Severe hepatic impairment (TB >3- 10 x ULN, any AST).**

Sponsor Response

Sponsor acknowledges the Agency's comments and will include an analysis using the NCI-ODWG criteria to classify patients into different hepatic impairment categories to evaluate their impact on PK of belinostat.

Discussion:

No discussion occurred.

- **We recommend you to refer to the following guidelines that describe the general expectations for submitting pharmacometric data and models (http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm).**

Sponsor Response

Sponsor acknowledges the Agency's comment and will review the specified guidelines.

Discussion:

No discussion occurred.

- **Although not clearly stated in the meeting package, we expect you to perform exposure-efficacy analysis for CLN-19 study independently as this is the relevant patient population for which the indication is being sought. In addition, both univariate and multivariate exposure-response analysis (adjusting for baseline risk factors) should be conducted.**

Sponsor Response

Sponsor agrees to perform an exposure-response analysis for the CLN-19 study as suggested by the Agency since it is the study relevant to the indication being sought.

Discussion:

No discussion occurred.

- **You should evaluate different exposure metrics (C_{min}, C_{max}, AUC) for their association with efficacy and safety endpoints.**

Sponsor Response

Sponsor proposes to perform these analyses for the CLN-19 study since, as discussed above, it is the study relevant to the indication sought.

Does the Agency agree?

Discussion:

The Agency clarified that the exposure metrics for safety can use CLN-19 and additional monotherapy studies that are relevant. However, the exposure metrics for efficacy should use CLN-19.

Question 3:

Based upon the agreement reached during the 20 July 2011 Type C Meeting, the Sponsor is initiating a new Mass Balance study of belinostat entitled, "*A Phase 1 Study for the Evaluation of Excretion (Mass Balance) and Pharmacokinetics of* ^{14}*C-Labeled Belinostat in Patients with Recurrent or Progressive Malignancy.*" The Sponsor proposes to submit data from the Mass Balance study as soon as they become available.

Does the Agency agree?

FDA Response to Question 3:

It is the agency's expectation that the NDA submission should be complete at the time of Original NDA submission. Submission of data during the review cycle should be avoided and is subject to extension of the PDUFA clock. For clinical pharmacology studies that cannot be completed prior to NDA submission, appropriate restrictions should be included in proposed labeling. If you commit to submitting the final report for the Mass Balance study within 30-days after filing the NDA application, the report will be reviewed with the first-cycle.

Sponsor Response

Sponsor acknowledges the Agency's response and will include any appropriate restrictions in the proposed labeling.

Discussion:

No discussion occurred.

Question 4:

The Sponsor initiated **Study 8846** in collaboration with NCI for the treatment of belinostat in patients with solid tumors and lymphoma with varying degrees of organ (hepatic) dysfunction. This study is currently enrolling patients.

The Sponsor plans to submit an interim report of safety and tolerability, as well as pharmacokinetic data for evaluable patients as of data cut off date of 30 Dec 2012, and will submit the final report as soon as it is available.

Does the Agency agree?

FDA Response to Question 4:

See response to Question 3 regarding expectations for a complete application. It is preferred that only final study reports are submitted for review. Interim study results should be included in the first cycle NDA review only if there is a serious safety signal that needs to be addressed in labeling.

Sponsor Response

The hepatic organ dysfunction study is being conducted in collaboration with NCI under the leadership of the Organ Dysfunction Group. Patients with progressive hepatic insufficiency are being recruited, and the Sponsor is not aware of any serious safety signal to date. Based on the guidance provided by the Agency, the Sponsor will not plan to submit an interim report for the ongoing hepatic organ dysfunction study.

Discussion:

No discussion occurred.

2.3. Clinical

Question 5:

The Sponsor intends to submit a clinical dossier consisting of clinical study reports (CSRs) for the **CLN-19** pivotal study and 13 additional supportive clinical studies as listed in Table 3. An overview of the Clinical program, including the **CLN-19** study results, is provided in Section 14.

For the NDA, all CSRs will be submitted in Module 5; the clinical summaries of efficacy [indication] and safety will be included in Modules 2.7.3 and 2.7.4, respectively. For the ISE and ISS, refer to Question 9 and Question 10 for the Sponsor's proposals. The Sponsor believes the clinical data package is sufficient to support the safety and efficacy of belinostat in the targeted indication.

Does the Agency agree?

FDA Response to Question 5:

Your proposal appears acceptable at this time. However, whether these studies will be sufficient to support the proposed indication will be a review issue.

Sponsor Response

Sponsor acknowledges the Agency's comments and has no further questions.

Discussion:

No discussion occurred.

Question 6:

Per agreement under the SPA process, **CLN-19** was considered the pivotal study and adequate to address the objectives necessary to support the safety and efficacy of belinostat for the proposed indication of the treatment of relapsed or refractory PTCL (b) (4) For the NDA submission, the Sponsor is planning to use a cut-off date of 31 Aug 2012 to provide a minimum of 12 months follow-up of safety and efficacy data from the first study treatment (Cycle 1, Day 1) for all patients, except for those deceased or lost to follow- up prior to the cut-off date. Refer to Section 14.2.1 for a summary of these top line clinical data and independent response assessment data from **CLN-19.**

Does the FDA agree?

FDA Response to Question 6:

No. Please note that both the response rate and duration of response will be taken into consideration for determination of efficacy.

We recommend a minimum of 6 months of follow-up for the last responding patient to ensure that the duration of response data is mature.

Sponsor Response

The Sponsor acknowledges the Agency's recommendations. By the proposed data cut-off date of 31 August 2012, all patients who responded per the Independent Review Committee had either progressive disease (PD) or were in response for >10 months, except for one patient. This patient had a documented partial response (PR) by Central Review, starting on 14 June 2012 with documented PD on 6 September 2012; one week after the proposed data cut-off date. Extending the data cut-off date by one week to include the disease progression of this patient would have no effect on the objective response rate or the

median duration of response. Therefore, the Sponsor proposes to keep the planned data cut-off date of 31 August 2012 for the analyses of data from the CLN-19 pivotal study. Standardized response criteria, including IWG (Cheson et al, JCO, 25:5, page 579-586 , 2007) will be applied to the belinostat data to provide uniform end points to allow for appropriate comparisons among PTCL clinical trials with other agents.

Discussion:

The sponsor's proposal for the data cut-off date is acceptable. The sponsor proposes to include in the NDA, analyses that compare various response criteria performance with Belinostat.

Question 7:

The Sponsor plans to submit the data generated by the independent Central Pathology Review Group (CPRG) in the **CLN-19** CSR, but not the forms generated during the CPRG review process. The PDF images of those forms will be available during the NDA review upon request.

Does the Agency agree?

FDA Response to Question 7:

No. Submit the forms.

Sponsor Response

Sponsor acknowledges the Agency's preference and will include the CPRG review forms in the NDA.

Discussion:

No discussion occurred.

Question 8:

The Sponsor plans to submit the assessment of response data by the Independent Review Committee (IRC) as tabular listings in the **CLN-19** CSR, but not the radiographic and photographic images used by the IRC to assess response. The PDF images of the scans shall be available from (b) (4) (previously known as (b) (4)) during the NDA review upon request.

Does the Agency agree?

FDA Response to Question 8:

Your proposal is acceptable.

Sponsor Response

Sponsor acknowledges the Agency's comments and has no further questions.

Discussion:

No discussion occurred.

Question 9:

Efficacy data for the target population of relapsed or refractory PTLC will be provided separately for the pivotal study (**CLN-19**) and supportive study (**CLN-6**). The primary basis of efficacy to support approval in the target indication will be **CLN-19**. The **CLN-19** statistical analysis plan (CLN-19 SAP) is provided in Section 5.3.5.2. The Sponsor plans to split the ISE as follows: the text portion will be placed in Module 2 (Section 2.7.3), and the appendices and datasets will be placed in the respective CSRs in Module 5. Only the datasets and related files will be submitted for **CLN-19** (Refer to Question 16).

Does the Agency agree?

FDA Response to Question 9:

No. Modules 2 and 5 have different purposes. Module 2 is a true summary. Module 2 should be a high level overview and should be a useful reference to the overall clinical findings for regulatory agency staff involved in the review of other sections of the marketing application. The Clinical Overview should (1) present the strengths and limitations of the development program and study results, (2) analyze the benefits and risks of the medicinal product in its intended use, and (3) describe how the study results support critical parts of the prescribing information. (From the Guidance for Industry M4E: the CTD – Efficacy)

Module 5 should contain text with detailed in depth discussion and analyses.

Sponsor Response

The Sponsor acknowledges the Agency's recommendation and plans to submit the Summary of Clinical Efficacy and the Integrated Summary of Efficacy in accordance to the ICH M4E guidance and the April 2009 FDA Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document.

As recommended in the FDA's response to Question 12, a Clinical Overview will also be included.

Discussion:

No discussion occurred.

Question 10:

The ISS SAP will be provided in Module 5.3.5.3. The ISS will integrate data from the company- sponsored studies in specific groupings of the safety data as discussed in Question 11. The Sponsor anticipates that the ISS will contain a total of less than 400 pages of text (with incorporated tables and figures) and therefore plans to split the ISS as follows: the text portion will be placed in Module 2 (Section 2.7.4), and the appendices and datasets will be placed in Module 5 (Section 5.3.5.3). Section 2.7.4 shall refer the reader to Section 5.3.5.3 for the appendices and datasets. Section 5.3.5.3 shall refer the reader to Section 2.7.4 for the text portion of the ISS.

FDA Response to Question 10:

No. Modules 2 and 5 have different purposes. Module 2 is a true summary. Module 2 should be a high level overview and should be a useful reference to the overall clinical findings for regulatory agency staff involved in the review of other sections of the marketing application. The Clinical Overview should (1) present the strengths and limitations of the development program and study results, (2) analyze the benefits and risks of the medicinal product in its intended use, and (3) describe how the study results support critical parts of the prescribing information. (From the Guidance for Industry M4E: the CTD – Efficacy)

Module 5 should contain text with detailed in depth discussion and analyses.

Sponsor Response

The Sponsor acknowledges the Agency's recommendation and plans to submit the Summary of Clinical Safety and the Integrated Summary of Safety in accordance to the ICH M4E guidance and the April 2009 FDA Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document.

As recommended in the FDA's response to Question 12, a Clinical Overview will also be included.

Discussion:

No discussion occurred.

Question 11:

Due to the differing entry criteria, the diverse patient populations and belinostat dose regimens (dose and schedule) for patients included in this filing, all safety data will not be pooled. Instead, safety data will be presented in summary tables by the proposed analysis populations (see Table 11), based on the ISS SAP. All patients receiving at least one dose of belinostat will be included in these analyses. The Sponsor proposes the following analysis populations for the safety data in the ISS:

Table 11 Analysis Populations

Group	Analysis Populations		Number of treated patients[a]	Studies
1	1	Belinostat monotherapy, 1000 mg/m^2	**129**	**CLN-19**
2	2	Belinostat Monotherapy, 150-1200 mg/m^2	**158** *46* *16* *25* *53* *18*	 ***TT20*** ***TT30*** ***301-G*** ***CLN-6*** ***CLN-20***
3	3A	Belinostat 1000 mg/m^2 + carboplatin/paclitaxel	**42**	**CLN-17**
	3B	Carboplatin/paclitaxel	**46**	**CLN-17**
4	4	Belinostat + combination therapy	**188** *35* *3* *80* *25* *41* *4*	 **CLN-4** **CLN-5** **CLN-8** **CLN-14** **CLN-15** **CLN-16**
5	5	Oral monotherapy	**120**	**CLN-9**

[a] total number of patient in each analysis population appear in **bold**, with numbers of patients in each trial appearing in *italic*.

Does the Agency agree?

FDA Response to Question 11:

Yes. Please also include the datasets for the proposed safety analysis population.

Sponsor Response

Sponsor acknowledges the Agency's comment and, as requested, will include the datasets for the proposed safety analysis populations in the NDA.

Discussion:

No discussion occurred.

Question 12:

In accordance with the April 2009 *Guidance for Industry, Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document*, Page 3, Table 1, Section 2.5 of eCTD, Clinical Overview, is not a U.S. requirement. In Section A on the same page, the Guidance also states: "An overview of efficacy and safety results can be included in Module 2". The Sponsor interprets this to mean that Section 2.5 is optional and may consist of links to the respective clinical summaries in Section 2.7 of the eCTD.

Does the Agency agree?

FDA Response to Question 12:

Although the Clinical Overview is not a requirement, we prefer that you include it in the NDA submission.

Sponsor Response

Sponsor acknowledges the Agency's preference and will include the Clinical Overview section in the NDA.

Discussion:

No discussion occurred.

Question 13:

For safety data from the ongoing studies that will be submitted in the 4-month safety update, the Sponsor proposes to use the date of the NDA submission as the cut-off date for the safety update. The 4-month safety update will include safety data for the ongoing clinical studies, including the **CLN-19** pivotal study, and all other ongoing studies.

Does the Agency agree?

FDA Response to Question 13:

Your proposal is acceptable.

Sponsor Response

Sponsor acknowledges the Agency's comments and has no further questions.

Discussion:

No discussion occurred.

Question 14:

The Sponsor proposes to submit complete CSRs for all of the studies listed in Table 3, with the exception of the **CLN-17** and **CLN-14** studies. For these two combination therapy studies, abbreviated CSRs including only safety data will be provided.

Does the Agency agree?

FDA Response to Question 14:

Yes.

Sponsor Response

Sponsor acknowledges the Agency's comment and has no further questions.

Discussion:

No discussion occurred.

Question 15:

For the pivotal **CLN-19** study, the Sponsor proposes providing case report forms (CRFs) for patients with serious adverse events (including deaths) within 30 days of the last dose of belinostat administration, and for patients who discontinued study treatment for adverse events. For all other studies in the dossier, CRFs will be available upon request.

Does the Agency agree?

FDA Response to Question 15:

Your proposal is acceptable.

Sponsor Response

Sponsor acknowledges the Agency's comment and has no further questions.

Discussion:

No discussion occurred.

Question 16:

The CLN-19 SAP will be provided in Module 5.3.5.2 and the ISS SAP will be provided in Module 5.3.5.3. The Sponsor plans to submit the following databases and related files:

- Study Data Tabulation Model (SDTM) datasets for the pivotal **CLN-19** study and ISS with corresponding define.xml files
- Analysis datasets for the pivotal study **CLN-19** and ISS with corresponding define.pdf files.

Does the Agency agree?

FDA Response to Question 16:

Yes.

Sponsor Response

Sponsor acknowledges the Agency's comment and has no further questions.

Discussion:

No discussion occurred.

Question 17:

For all clinical studies with belinostat sponsored under the INDs of the NCI and other investigators (N=16) for which the Sponsor does not have the primary datasets, we propose to provide only the available publications except for the NCI-8846 hepatic impairment study.

Does the Agency agree?

FDA Response to Question 17:

Provide a list of the 16 studies you will only provide publications for. For any study results that you will use to support labeling claims the sponsor should obtain the primary data sets and they should be included with the NDA.

Sponsor Response

Sponsor acknowledges the Agency's request and the NDA will include a list of studies for which we will only be providing publications. None of these studies will be used to support labeling claims.

Discussion:

No discussion occurred.

Question 18:

The Risk Management Plan will be provided in Module 1.16 of the NDA. The Sponsor believes the potential risks identified in the premarketing risk assessment will be adequately described in the Prescribing Information that provides instructions for dose modifications to manage hematological toxicities and non-hematological treatment-related toxicities. Further, a patient information insert will be provided that advises patients on when they should talk to their doctor regarding potential serious events. Finally, the Sponsor will have postmarketing data collection and risk assessment processes in place to further evaluate the product's risk profile. For the oncology patient population, the above activities are considered adequate to minimize risks post-approval for patients treated with belinostat.

Does the Agency agree?

FDA Response to Question 18:

No. Whether additional safety related actions are needed will be determined during the review of the NDA.

Sponsor Response

Sponsor acknowledges the Agency's comment and has no further questions.

Discussion:

No discussion occurred.

Question 19:

The Sponsor plans to cross-reference any files that have been submitted previously in electronic format to Belinostat IND 070789 and that support the information in the NDA. These files would be listed in Section 1.4.4 of the NDA and would not be resubmitted.

Does the Agency agree?

FDA Response to Question 19:

No. Provide the details of the files that you propose to cross-reference.

Sponsor Response

Sponsor acknowledges the Agency's comment and will include all files in the NDA submission.

Discussion:

No discussion occurred.

Question 20:

The Sponsor believes the NDA is eligible for priority review.

Does the Agency agree?

FDA Response to Question 20:

No. The review priority will be decided at the time of filing. You should submit your justification for priority review with the NDA submission.

Sponsor Response

Sponsor acknowledges the Agency's comment and will include a justification for priority review in the NDA submission.

Discussion:

No discussion occurred.

Question 21:

A draft high level eCTD Table of Contents pertaining to the nonclinical, clinical, and administrative sections of the proposed NDA is provided in Appendix 1 of this Briefing Package.

The eCTD Table of Contents for the chemistry, manufacturing and controls (CMC) sections of the NDA will be discussed during the 08 May 2013 CMC pre-NDA Meeting with the Agency.

Does the Agency have any comments on the proposed organization of the NDA submission?

FDA Response to Question 21:

The proposed outline organization of the NDA in Appendix 1 is acceptable.

You have not provided information on your planned data submission contents. Please review the additional comments for data submission.

Sponsor Response

Sponsor acknowledges the Agency's comment. The planned data submission files will include SDTM datasets for CLN-19 and ISS, ADaM datasets for CLN-19 and ISS; the programs for all efficacy variables and table outputs for CLN-19.

Discussion:

No discussion occurred.

Additional Clinical Comment:

1. Please be aware that time to event endpoints such as PFS and OS are not interpretable in a single arm trial and no labeling claims can be made based on these endpoints.

Sponsor Response

Sponsor acknowledges the Agency's comment.

Discussion:

No discussion occurred.

Additional Statistical Comments:

1. The SAS programs that are used to create the derived datasets for the efficacy endpoints and the SAS programs that are used for efficacy data analysis should be included in the NDA submission.
2. Please provide the location of the SAS dataset, the names of the variables used and the programs used to get every new value that will be appearing in the label.

Sponsor Response

1. ***Sponsor acknowledges the Agency's guidance and plans to submit all SAS programs that were used to create the derived datasets for the efficacy endpoints and the SAS programs that were used for efficacy data analyses in the NDA submission.***
2. ***The location of the SAS datasets, names of the variables used and the programs used to derive any new values in the label will also be included.***

Discussion:

No discussion occurred.

Additional Clinical Pharmacology Comments:
In the appropriate clinical pharmacology sections of the eCTD include the following:

- An evaluation of the effects of covariates such as age, weight, gender, race, etc. on the PK (pharmacokinetics) of belinostat.
- Datasets for clinical pharmacology and biopharmaceutics studies should be complete and not be limited to PK/PD. For example, domains related to safety (e.g., ADR's), demographics, non-PK laboratory values, concomitant drug use should be included. All of these are important in identifying patterns of potential clinical pharmacology related causes of clinical safety outcomes.
- Provide all concentration-time and derived PK parameter datasets for all studies. In the study reports, present the PK parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate.
- Provide a table listing of patients with renal or hepatic impairment who have received belinostat, organized by trial number. Include available renal and hepatic function parameters such as SCr, CLCr calculated by the Cockcroft Gault equation (or eGFR calculated by MDRD), AST/ALT, T.Bili, platelet count, etc for each patient in the listing. Also, provide summaries of the following information for each patient: PK and PD data, safety, and clinical efficacy.

Sponsor Response

Sponsor acknowledges the Agency's comments and will address them in the NDA submission.

Discussion:

No discussion occurred.

Additional Data Submission Comments:
The Agency prefers Spectrum Pharmaceuticals to submit datasets based on the Study Data Specifications version published at the time of submission (currently 2.0). However, in general, the Agency accepts datasets, which comply, within a reasonable timeframe, with previous versions of the Study Data Specifications and other related guidance; based on the timing of protocol design, protocol initiation, and data collection.

The Agency expects Spectrum Pharmaceuticals to evaluate the risk involved converting study data collected to standardized data, if applicable. The Agency prefers Spectrum Pharmaceuticals to submit study data conversion explanation and rationale. The study data conversion rationale and explanation should address either scenario; decision rationale for not converting or decision rationale for converting. The Agency expects Spectrum Pharmaceuticals's evaluation and rationale include study data scientifically relevant to the application's safety and efficacy representation. As such, the evaluation and explanation may include rationale based on the pooling/integrating of data from multiple studies.

The *PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2013 THROUGH 2017* guidance provides specific requirements for electronic

submissions and standardization of electronic drug application data. Spectrum Pharmaceuticals should design and implement data standardization in all research protocols to be included in regulatory submissions, as required based on the timing for implementation of the research. The non-clinical and clinical research study designs should include concise and complete explanation for implementation of data standardization in the data collection section of the protocol. Spectrum Pharmaceuticals should use the Clinical Data Interchange Standards Consortium (CDISC) Technical Road Map to design end-to-end harmonized data standardization, including the Clinical Data Acquisition Standards Harmonization (*CDASH*) standard for design and implementation of data collection instruments.

The Agency's methodology and submission structure supports research study design, as indicated in the *Guidance to Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* and the *Study Data Specifications.* The Agency's methodology and submission structure also supports integrating study data collection for Safety and Efficacy study submission. Each study should be complete and evaluated on its own merits. Spectrum Pharmaceuticals should maintain study data independently in the SEND datasets for non-clinical tabulations, SDTM datasets for clinical tabulations, and ADaM datasets for analyses tabulations. (See *SEND*, *SDTM* and *ADaM* as referenced in *Study Data Specifications).* Study analyses datasets should be traceable to the tabulations datasets.

In addition, Spectrum Pharmaceuticals should reference the *CDER Common Data Standards Issues Document* for further information on data standardization in submissions.

Additional Links:

Electronic Regulatory Submissions and Review Helpful Links
Electronic Common Technical Document (eCTD)
Study Data Standards Resources

Sponsor Response

Sponsor acknowledges the Agency's guidance and plans to submit datasets that were converted to SDTM version 1.2, using SDTM Implementation Guide version 3.1.2 and its Amendment 1. A BlankCRF.pdf file, annotated for SDTM domain will be submitted along with a spreadsheet with a tab for each SDTM domain, explaining CDISC mapping of the CRF data.

Discussion:

No discussion occurred.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our February 14, 2013 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

  The sponsor proposes to submit a complete application at the time of filing with the exception of study report and data sets for study CLN-20, which will be submitted within 30 days of application submission.

  All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application

- A preliminary discussion on the need for a REMS was held and it was concluded that the sponsor does not believe that a REMS would be required at this time. The Agency will determine the need for a REMS upon review of the data.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:

  Clinical Pharmacology
  The study report and data sets for study CLN-20 will be submitted within 30 days of NDA submission.

  Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

  NDA NUMBER: LATE COMPONENT - BIOMETRICS
  NDA NUMBER: LATE COMPONENT - CLINICAL
  NDA NUMBER: LATE COMPONENT - CLINICAL PHARMACOLOGY
  NDA NUMBER: LATE COMPONENT - NONCLINICAL
  NDA NUMBER: LATE COMPONENT - QUALITY

In addition, we note that a chemistry pre-submission meeting was scheduled to be held on May 8, 2013 and then withdrawn. We refer you to the preliminary comments for that meeting for any additional agreements that may have been reached.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Further, under the Food and Drug Administration Safety and Innovaton ACT (FDASIA), sponsors must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

Discussion:

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the following labeling review resources: the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, labeling guidances, and a sample tool illustrating the format for Highlights and Contents (Table of Contents) available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

See attached slide listing Sponsor Participants.

List of Sponsor Participants

Name	Title
Rajesh C. Shrotriya, MD	Chairman, Chief Executive Officer, and President (Spectrum)
Lee F. Allen, MD, PhD	Chief Medical Officer (Spectrum)
Steven Fruchtman, MD	Senior Vice President, Clinical Research Hematology/Oncology (Spectrum)
Shanta Chawla, MD	Vice President, Clinical Research (Spectrum)
Guru Reddy, PhD	Vice President, Preclinical Research and Development (Spectrum)
Nozar Azarnia, PhD	Vice President, Biostatistics and Data Management (Spectrum)
Anil K. Hiteshi, RAC	Vice President, Global Regulatory Affairs (Spectrum)
Anne Sillemann, M.Sc., Pharm.	Director of Global Regulatory Affairs (Topotarget)
Gisela Schwab, MD	Board Member (Topotarget)

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/s/

VIRGINIA E KWITKOWSKI
06/05/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 70,789

TopoTarget USA, Inc.
Attention: Ms. Alyssa Carter
Senior Manager Regulatory Affairs
100 Enterprise Drive, Suite 505
Rockaway, NJ 07866

Dear Ms. Carter:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for belinostat (PXD101).

We also refer to your July 24, 2008, request, serial number 0144, on July 25, 2008, for a special protocol assessment for a clinical protocol. Protocol PXD101-CLN-19 is titled "A Multicenter, Open-Label Trial of Belinostat in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma."

We note that this protocol includes revisions discussed in our June 12, 2008, letter and our January 11, and July 21, 2008 minutes.

A special protocol assessment is designed to evaluate an individual protocol primarily in response to specific questions posed by the sponsor. Our assessment does not address your overall development strategy. Based on our review of your questions in the context of other submitted information, we agree that the design and planned analysis of your study adequately address the objectives necessary to support a regulatory submission.

We have the following responses (**bolded font**) to your questions.

1. Is the design, including inclusion and exclusion criteria, as described in the clinical trial protocol PXD101-CLN-19 (version 2.0, 23 July 2008), "*A Multicenter, Open-Label Trial of Belinostat in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma*", acceptable to the Agency?

FDA Response: Yes.

2. Is the statistical design, including analyses, as described in the Statistical Analysis Plan (version 2.0, 23 July 2008) for study PXD101-CLN-19, acceptable to the Agency?

FDA Response:

The proposed statistical design and analyses are acceptable. Please note that a clinically meaningful and statistically persuasive effect on response rate with reasonable duration of response and an acceptable safety profile may be considered for a regulatory decision.

3. Is the setup, including definition of procedures, of the independent radiology review as described in the Independent Review Charter, Radiology (version 1.0, Sponsor Draft version 5.0, 23 July 2008) for study PXD101-CLN-19, acceptable to the Agency?

FDA Response:

The Office of Oncology Drug Products has implemented new interim procedures for Special Protocol Assessments of clinical protocols. These new procedures do not include detailed review of radiology review charters, nor are they subject to SPA agreements. The quality of the proposed radiology review charter is your responsibility.

4. Is the setup, including role description, of the data monitoring committee as described in the Charter for the Data Monitoring Committee (DMC) (version 1.0, 17 July 2008) for study PXD101-CLN-19, acceptable to the Agency?

FDA Response:

The Office of Oncology Drug Products has implemented new interim procedures for Special Protocol Assessments of clinical protocols. These new procedures do not include detailed review of Data Monitoring Committee charters, nor are they subject to SPA agreements. The quality of the proposed DMC charter is your responsibility.

5. Is the setup, including definition of procedures, for the central pathology review as described in the Charter for the Central Pathology Review Group (CPRG) (version 1.0, 18 July 2008) for study PXD101-CLN-19, acceptable to the Agency?

FDA Response: Yes.

6. Based on the above described development plan for belinostat, is the planned exposure in study PXD101-CLN-19 of a total of at least 100 evaluable patients (i.e. patients with a diagnosis of peripheral T-cell lymphoma confirmed at central review and treated with at least one dose of belinostat) within the study, adequate to form the basis of approval for registration of belinostat in the treatment of patients with peripheral T-cell lymphoma, provided the magnitude, duration and quality of the achieved objective response rate is sufficient, and an acceptable safety profile is shown?

FDA Response: This will be a review issue.

In addition, we have the following comments.

1. **The trial activities chart (Appendix C) indicates that blood chemistries will be evaluated at baseline, on days 1 & 5, and days 11-15. The chemistry row references note #6 which does not clarify the schedule for "days 11-15". Please add a clarification to note #6 that the chemistry evaluation will occur "once during days 11-15" as you did in the CBC schedule. Your agreement to clarify this will be adequate.**

2. **Protocol PXD101-CLN-19 is acceptable from a Clinical Pharmacology perspective.**

New public health concerns or changes in your development program may affect our agreement on the acceptance of the protocol. Also, our agreement is limited to the major design features (i.e., patient population, choice of control, primary efficacy endpoint(s), safety monitoring plan, and statistical analysis plan) and the issues addressed in our comments above. You are responsible for assuring that the design, conduct, recording, and reporting of this clinical trial complies with standards for good clinical practice (GCP) necessary to support a regulatory submission.

We advise you that, if you make any changes to this protocol, this agreement may be invalidated. This agreement is subject to modification only as outlined in section 505(b)(4)(C) of the Act (see *Guidance for Industry: Special Protocol Assessment*).

If you have any questions, call Brenda Atkins, Consumer Safety Officer, at 301-796-1324.

Sincerely,

{See appended electronic signature page}

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

Linked Applications	Sponsor Name	Drug Name
IND 70789	TOPOTARGET USA INC	PXD101

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/s/

ROBERT L JUSTICE
09/04/2008

TELECOM MINUTES

MEETING DATE: November 29, 2007 **TIME:** 2:30 PM **LOCATION:** 2201 WO

IND: 70,789 **Meeting Request Submission Date:** October 3, 2007(0099)
Briefing Document Submission Date: October 31, 2007(0104)
Supplemental Briefing Document Date: November 15, 2007(0106)

DRUG: belinostat (PXD101), intravenous

INDICATION: Peripheral T Cell Lymphoma

SPONSOR: CuraGen Corporation

TYPE of MEETING: End-of-Phase 2 Type B Meeting

FDA PARTICIPANTS, TITLES AND OFFICES (bolded):

Robert L. Justice, M.D., Director, Center for Drug Evaluation and Research (CDER)/Office of New Drugs (OND)/Office of Oncology Drug Products (OODP)/Division of Drug Oncology Products (DDOP)
Virginia Kwitkowski, M.D., Medical Officer, CDER/OND/OODP/DDOP
Rajeshwari Sridhara, Ph.D., Team Leader, DBV/OB/CDER/FDA
Janet Jiang, Ph.D., Biometrics Reviewer, DBV/OB/CDER/FDA
Brenda Atkins, Project Manager, DDOP

INDUSTRY PARTICIPANTS AND TITLES:

Beth Crowley, B.S., VP, Clinical Strategy and Planning
Henri Lichenstein, Ph.D., Vice President, Product Development
Chean Eng Ooi, Ph.D., Assistant Director, Clinical Research
Timothy Shannon, M.D., CEO
Ronit Simantov, M.D., Vice President-Medical
Mary Taylor, MPH, Senior Vice President, Regulatory Affairs

MEETING OBJECTIVES:

To discuss the adequacy of the safety and efficacy evaluation of belinostat [redacted] (b) (4)

BACKGROUND:

According to the sponsor, an overall clinical program of intravenous (IV) belinostat (PXD101) includes a total of (b) (4) clinical trials, (b) (4) sponsored by CuraGen and TopoTarget and (b) (4) sponsored by the National Cancer Institute-Clinical Trials Evaluation Program (NCI-CTEP). (b) (4) The registrational development plan includes a single multinational, multi-center, open-label, single arm study of IV belinostat in patients with relapsed or refractory peripheral T cell lymphoma (PTCL) (b) (4)

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1.1 **Clinical**

1. Objective Response Rate (ORR) measured by International Working Group Response Criteria (Cheson 2007) has been selected as primary endpoint, with at least a 20% response rate defined as clinically meaningful benefit. Positron Emission tomography (PET) scans will not be included. Progression Free Survival (PFS) and overall survival will be secondary endpoints in the study. Are the choices of primary and secondary endpoints acceptable to the Agency?

FDA Response:

Objective response rate is acceptable as a primary endpoint. The significance of ORR is assessed by its magnitude and duration, the percentage of complete responses, and an acceptable risk/benefit ratio. The results of time to event endpoints, such as PFS and OS in a single arm study are not interpretable and should be considered as exploratory. We refer you to the FDA guidance "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" www.fda.gov/cder/guidance/1397fnl.pdf

2. Assuming a two-sided alpha of 0.05 and power of 90%, approximately (b) (4) patients will be enrolled. The criteria for a positive trial are defined as an observed response rate of at least 20% with the lower boundary of the corresponding 95% confidence interval excluding 5%. A formal interim analysis will be conducted to evaluate efficacy and safety. Does the FDA agree with the statistical criteria as outlined?

FDA Response:

The proposed enrollment of (b) (4) patients is not likely to adequately assess the efficacy of the investigational agent. We encourage you to enroll a larger number of patients. You should consider selecting a higher lower boundary for the confidence interval. Additionally, please confirm that the analysis planned after (b) (4) patients for futility and safety is the same as this formal interim analysis. See also FDA response to question #1 above.

Discussion:

The sponsor requested clarification on the sample size requirement and the comment on the lower bound of the 95% confidence interval of the response rate. The FDA clarified that in general, 100 patients would be required for this indication. (b) (4) ***The sponsor understands the FDA's position. FDA clarified that the comment regarding the lower bound of the 95% confidence interval was related to the sample size and expected response rate.***

3. Pathology based eligibility (see inclusion criteria) at time of randomization will be based on pathology review at the local institution. Is this acceptable to the Agency?

FDA Response:

Local institution pathology confirmation is acceptable, but you must include adequate minimum pathology evaluation parameters in the protocol required for the diagnosis of each patient. Please plan to capture these pathology evaluation parameters in Case Report Forms.

1.2 **Regulatory**

1. Upon completion of this registrational trial in PTCL, approximately (b) (4) patients will have been treated with belinostat IV in all trials combined (CuraGen and NCI trials). About 2/3 of these patients will have been exposed to PXD101 at the MTD. We believe that this exposure provides sufficient safety information for registration of belinostat. Does the Agency agree?

FDA Response:

Yes, this appears to be acceptable; however, the adequacy of the safety population will be a review issue at the time of NDA submission.

2. Given the significant unmet medical need for therapy for PTCL and the epidemiology of the disease, we plan to conduct a single, uncontrolled (b) (4) study in patients with refractory or recurrent PTCL. We believe this should be sufficient for approval of belinostat in this indication. Does the Agency agree?

FDA Response:

No. A single, small, one-arm trial in PTCL is not likely to be considered adequate to support an NDA in this indication. In addition, for a single trial to support an NDA, the trial should be well designed, well conducted, internally consistent, and provide statistically persuasive efficacy findings so that a second trial would be ethically or practically impossible to perform. See FDA response to question #2 in Clinical 9.1.

Discussion:

See discussion above regarding clinical question 2.

3. We intend to file for orphan drug designation and therefore in accordance with 21 CFR 314.55(d) it is our understanding that pediatric data are not required. Does the Agency agree?

FDA Response:

Determinations as to Orphan Product Designation (OPD) are made by the Office of Orphan Products Development, not this Division. For further information regarding application for OPD, please consult the FDA web site at http://www.fda.gov/orphan. If you receive an OPD, then the PRE Act would not apply.

If you do not receive OPD, you may request a waiver or deferral of pediatric study requirements by submitting adequate justification.

Additional Comments:

1. **Please add "negative pregnancy test for women of childbearing potential" to Section 3.2.1 Inclusion Criteria.**
2. (b) (4)
3. (b) (4)
4. **The planned CT imaging does not incorporate imaging of the neck, a common site of lymphoma involvement. Please consider imaging the neck at baseline and during follow-up.**
5. **Given the preliminary evidence of QT prolongation in previous studies, we recommend this study include more frequent ECG monitoring** (b) (4) **You should consider doing ECG monitoring at the end of infusion day 5 each cycle for every patient.**
6. **We recommend that you collect sparse pharmacokinetic samples in all patients and explore the exposure-response relationships for belinostat and any active**

metabolites, for measures of both effectiveness and toxicity. Please refer to http://www.fda.gov/cder/guidance/5341fnl.pdf for more information.

7. **Given the fact that belinostat inhibits CYP2C9 and CYP2C8 in vitro, we recommend that you conduct clinical studies to evaluate if belinostat alters the metabolism of a sensitive CYP2C9 substrate (for example, S-warfarin). If significant interaction is demonstrated, additional clinical studies to evaluate if belinostat alters the metabolism of a sensitive CYP2C8 substrate (for example, repaglinide) may be needed. Please refer to <http://www.fda.gov/cder/guidance/6695dft.pdf> for more information.**

8. **The completeness of your QT study cannot be determined without reviewing your data. Please submit the study reports to the IND for review by the IRT/QT group as soon as possible (preferably before the conduct of the major study for marketing approval).**

   In order for us to adequately review the QT effect of belinostat, please submit the following:

   - **Electronic copies of reports for the studies from which ECG data were analyzed**
   - **Electronic copies of the clinical protocols for the studies PXD101-CLN-4 and PXD101-CLN-9 as well as other studies from which ECG s were analyzed**
   - **Annotated CRFs**
   - **Interim reports of analyses of ECG data**
   - **Electronic data sets as SAS transport files**
   - **A Define file which describes the contents of the electronic data sets**
   - **All statistical programs with analysis datasets that were used to analyze study endpoints as well as to perform any exposure-response analysis**
   - **ECGs submitted to the ECG warehouse**
   - **Detailed summary of dose-response and exposure response analyses**

9. **Provide a concise pharmaceutical development report in the NDA highlighting the product development and process understanding in the delineation of critical quality attributes and critical process parameters. Also, you are encouraged to take the quality-by-design (QbD) approach to pharmaceutical development as outlined in ICH Q8 Guidance on *Pharmaceutical Development.* If appropriate, please include QbD-related information and questions in a CMC-specific meeting or request a CMC guidance meeting to discuss your QbD approach during the conduct of your major study(s) intended to support the NDA.**

10. **We recommend that for the NDA, the stability data be submitted in SAS transport format along with statistical analyses of all stability indicating attributes.**

FINAL PROTOCOLS:

If you plan on submitting a request for Special Protocol Assessment, please refer to the May 2002 "*Guidance for Industry – Special Protocol Assessment"* (posted on the Internet 5//2002) and submit final protocol(s) to the IND for FDA review as a REQUEST FOR SPECIAL PROTOCOL ASSESSMENT (SPA) in bolded block letters at the top of your cover letter. Also, the cover letter should clearly state the type of protocol being submitted (i.e., clinical) and include a reference to this EOP2 meeting. A sample case report form (CRF), the statistical analysis plan, the independent radiologic review charter (if applicable), and the independent data monitoring committee charter should be included. 10 desk copies of this SPA should be submitted directly to the project manager.

Since we may use our ODAC consultant for this protocol review, and their clearance takes several weeks, we would appreciate any lead-in time you could give us as to when the SPA will be submitted. You should also be aware that our using a consultant extends the due date on these SPAs until 45 days after we receive the consultant's written comments.

SUBMISSION OF CLINICAL TRIALS TO NIH PUBLIC ACCESS DATA BASE:

Section 113 of the Food and Drug Modernization Act (Modernization Act) amends 42 U.S.C. 282 and requires the establishment of a public resource for information on studies of drugs for serious or life-threatening diseases conducted under FDA's Investigational New Drug (IND) regulations (21 CFR part 312). The National Institutes of Health (NIH) through its National Library of Medicine (NLM), and with input from the FDA and others, developed the Clinical Trials Data Bank, as required by the Modernization Act.

FDA has made available a final guidance to implement Section 113 of the Modernization Act. The guidance describes the type of information to submit and how to submit information to the Clinical Trials Data Bank. The guidance entitled "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions" was made available on March 18, 2002. It is accessible through the Internet at http://www.fda.gov/cder/guidance/4856fnl.htm

The clinical trial information for the Clinical Trials Data Bank should include the purpose of the trial, the patient eligibility criteria, the location of the trial sites and, a contact for patients wanting to enroll in the trial. The data fields and their definitions are available in the Protocol Registration System at http://prsinfo.clinicaltrials.gov/. Protocols listed in this system by will be made available to the public on the Internet at http://clinicaltrials.gov.

If you have any questions, contact Theresa Toigo at (301) 827-4460 or 113trials@oc.fda.gov.

FINANCIAL DISCLOSURE FINAL RULE:

We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective and any study in which a single investigator makes a significant contribution to demonstration of safety.

Please refer to the March 20, 2001 "*Guidance for Industry: Financial Disclosure By Clinical Investigators*" (posted on the Internet 3/27/2001) at http://www.fda.gov/oc/guidance/financialdis.html.

PEDIATRIC RESEARCH EQUITY ACT (PREA):

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

PEDIATRIC EXCLUSIVITY:

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

DEMOGRAPHICS:

In response to a final rule published 2-11-98, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data "by gender, age, and racial subgroups" in an NDA. Therefore, as you are gathering your data and compiling your NDA, we request that you include this analysis. To assist you in this regard, the following table is a suggestion for presentation of the numeric patient demographic information. This data, as well as the pertinent analyses, should be provided in the NDA.

Please provide information for each category listed below from the primary safety database excluding PK studies.

CATEGORY		NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG
Gender	Males		All Females		Females >50	
Age:	0-≤1 Mo.		>1 Mo.-≤ 2Year		>2-<12	
	12-16		17-64		≥65	
Race:	White		Black		Asian	
	Other					

ACTION ITEMS:

Please refer to the Agency's responses and comments above.

see electronic signature page
Brenda Atkins
Project Manager
(signed paper version 12-17-07)

Concurrence Chair: see electronic signature page
Robert L. Justice, M.D.
Director, Division of Drug Oncology Products
(signed paper version _____)

5 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

Linked Applications	Sponsor Name	Drug Name
IND 70789	CURAGEN CORP	PXD101

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/s/

BRENDA J ATKINS
12/17/2007

ROBERT L JUSTICE
12/19/2007

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206256

LATE-CYCLE MEETING MINUTES

Spectrum Pharmaceuticals, Inc.
Attention: Anil K. Hiteshi, RAC
Vice President, Global Regulatory Affairs
157 Technology Drive
Irvine, CA 92618

Dear Mr. Hiteshi:

Please refer to your New Drug Application (NDA) dated December 8, 2013, received December 9, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Beleodaq™ (belinostat) for Injection.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on June 4, 2014.

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

If you have any questions, call Jessica Boehmer, Regulatory Project Manager at (301) 796-5357.

Sincerely,

{See appended electronic signature page}

Virginia Kwitkowski, MS, RN, ACNP-BC
Lead Clinical Analyst, Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: June 4, 2014, 10:00 AM – 11:00 AM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1419
Silver Spring, Maryland 20903

Application Number: NDA 206256
Product Name: Beleodaq™ (belinostat) for Injection
Applicant Name: Spectrum Pharmaceuticals, Inc.

Meeting Chair: Virginia Kwitkowski, MS, RN, ACNP-BC
Meeting Recorder: Jessica Boehmer, MBA

FDA ATTENDEES

Division of Hematology Products (DHP)
Ann Farrell, MD, Division Director
Edvardas Kaminskas, MD, Deputy Director
Robert Kane, MD, Deputy Director for Safety
Virginia Kwitkowski, MS, RN, ACNP-BC, Clinical Team Leader
Hyon-Zu Lee, PharmD, Clinical Reviewer
Toni-Ann Cox, Regulatory Project Manager
Ebla Ali Ibrahim, MS, Team Leader, Project Management
Patricia Garvey, RPh, Senior Regulatory Project Manager
Diane Leaman, BS, Safety Regulatory Project Manager
Jessica Boehmer, MBA, Senior Regulatory Project Manager

Division of Hematology Oncology Toxicology (DHOT)
Pedro De Valle, PhD, Pharmacology/Toxicology Reviewer
Stacey Ricci, PhD, Pharmacology/Toxicology Reviewer

Office of Clinical Pharmacology (OCP)
Julie Bullock, PharmD, Clinical Pharmacology Team Leader
Bahru Habtemariam, PharmD, Clinical Pharmacology Reviewer
Michael Pacanowski, PhD, Associate Director for Genomics and Targeted Therapy Group
Rosane Charlab Orbach, PhD, Acting Team Leader, Genomics and Targeted Therapy Group
Sarah Dorff, PhD, Genomics Reviewer, Genomics and Targeted Therapy Group

Office of Biostatistics (OB), Division of Biometrics V (DB)
Yuan-Li Shen, PhD, Statistical Team Leader
Erik Bloomquist, PhD, Statistical Reviewer

Office of Surveillance and Epidemiology (OSE)/Office of Pharmacovigilance and Epidemiology (OPE) /Division of Pharmacovigilance (DPV)
Wana Manitpisitkul, PharmD, Safety Evaluator

Office of Prescription Drug Promotion (OPDP)
James Dvorsky, PharmD, Senior Regulatory Reviewer

Office of New Drug Quality Assessment (ONDQA)
Janice Brown, MS, CMC Lead
Xiao-Hong Chen, PhD, CMC Reviewer

Office of Compliance (OC)/Division of Manufacturing and Product Quality (DMPQ)
Vipul Dholakia, Compliance Officer

Office of Planning and Informatics (OPI)
Kimberly Taylor, Operations Research Analyst

EASTERN RESEARCH GROUP ATTENDEES
(b) (6)

APPLICANT ATTENDEES
Rajesh C. Shrotriya, MD, Chairman, Chief Executive Officer, and President
Lee F. Allen, MD, PhD, Chief Medical Officer
Gajanan Bhat, PhD, Executive Director, Biostatistics, Data Management and Medical Writing
Guru Reddy, PhD, Vice President, Preclinical R&D
Mi Rim Choi, MD, Director, Clinical Research
Pramod K. Gupta, PhD, Vice President, Pharmaceutical Operations
Anil K. Hiteshi, RAC, Vice President, Global Regulatory Affairs
Anne Sillemann, M.Sc., Pharm, Head of Global Regulatory Affairs (Topotarget)
Karsten Witt, MD, Board Member (Topotarget)

1.0 BACKGROUND

NDA 206256 was submitted on December 8, 2013, received on December 9, 2013 for Beleodaq™ (belinostat) for Injection.

Proposed indication: Treatment of Patients with Relapsed or Refractory Periperal T-Cell Lymphoma

PDUFA goal date: August 9, 2014

FDA issued a Background Package in preparation for this meeting on May 15, 2014.

2.0 DISCUSSION

1. Introductory Comments

Virginia Kwitkowski made an introductory statement regarding the meeting objectives. The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

2. Postmarketing Requirements/Postmarketing Commitments

Discussion:

PMR #1 (Phase I trial to establish the optimal safe dose of belinostat in combination with the CHOP regimen): Spectrum requests that the trial completion milestone be changed from December 2014 to June 2015. They also request that the final report submission milestone be changed from March 2015 to April 2016. (b) (4) The changes in trial completion and final report submission dates, however, will not impact the initiation of the PMR #2 trial since the results from both the Fol/CHOP and Bel/CHOP Phase 1 studies are required before proceeding with PMR #2. The Agency will discuss the proposed edit internally and respond to the Applicant in writing.

PMR #2 (Confirmatory Three-Arm Trial): Spectrum proposed to change the trial description to be consistent with the design of the PMR #2 study as requested during the Beleodaq NDA orientation meeting by the FDA. The design was to compare each experimental combination to CHOP and specifically not to compare the two experimental combinations to one another. Spectrum proposed to revise the PMR# 2 description from "Characterize the comparative efficacy and safety of Beleodaq when used in combination with a treatment regimen such as CHOP vs. pralatrexate plus CHOP, versus CHOP alone, for the initial therapy of patients with PTCL" to (b) (4) ". As the intention of this confirmatory trial (for the Beleodaq NDA) is to evaluate the addition of Beleodaq to CHOP compared to CHOP alone, the Agency agreed with the Applicant's proposed revision. No proposed changes to the milestone dates for this PMR were discussed.

PMR #3 (Mass Balance Study): No discussion was held on this PMR.

PMR #4 (Hepatic Impairment Study): Spectrum stated that they will continue to work with NCI, who is responsible for conducting this study. (b) (4) The Agency stated to Spectrum that though NCI may be conducting the study, Spectrum is ultimately responsible for the study conduct. The trial completion will be revised to December 2015.

PMR #5 (Renal Impairment Study): No discussion was held regarding PMR #5.

PMR #6 (Drug-Drug Interaction Study with strong UGT1A1 inhibitors): No discussion was held.

PMR #7: (Study of the interaction of belinostat in patients with wild-type, heterozygous and homozygous UGT1A1*28 genotypes): (b) (4)

The Agency provided a recommendation that both PMRs 6 and 7 could be addressed in a single trial. The sponsor could conduct a trial that evaluates the influences of strong UGT1A1 inhibitor and UGT1A1 polymorphismpectrum (b) (4)

3. Major Labeling Issues

Discussion:

There was discussion regarding the duration of response definitions and data that are appropriate for labeling. The Agency will continue internal discussion and have further communications with the Applicant regarding this endpoint.

Regarding the inclusion of response rates by subgroup, the Applicant proposed to include RR for the NOS and AITL groups in text only. The Agency will discuss internally and respond via labeling negotiations.

(b) (4)

The Agency will discuss internally and respond via labeling negotiations.

4. Review Plans

Discussion:

The Review Team plans to take action on or before the PDUFA Goal Date of August 9, 2014.

5. Wrap-up and Action Items

Discussion:

Spectrum will respond regarding the proposed combined PMR.

The Agency will respond to the Applicant's proposed labeling edits.

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/

VIRGINIA E KWITKOWSKI
06/10/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206256

LATE CYCLE MEETING
BACKGROUND PACKAGE

Spectrum Pharmaceuticals, Inc.
Attention: Anil K. Hiteshi, RAC
Vice President, Global Regulatory Affairs
157 Technology Drive
Irvine, CA 92618

Dear Mr. Hiteshi:

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

We also refer to the Late-Cycle Meeting (LCM) scheduled for June 4, 2014. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Jessica Boehmer, Regulatory Project Manager, at (301) 796-5357.

Sincerely,

{See appended electronic signature page}

Virginia Kwitkowski, MS, RN, ACNP-BC
Lead Clinical Analyst, Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: June 4, 2014, 10:00 AM – 11:00 AM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1419
Silver Spring, Maryland 20903

Application Number: NDA 206256
Product Name: Beleodaq™ (belinostat) for Injection
Indication: Treatment of Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma
Sponsor/Applicant Name: Spectrum Pharmaceuticals, Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

No substantive review issues have been identified to date.

ADVISORY COMMITTEE MEETING

Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/CDTL)
    - Welcome
    - Introductions,
    - Ground rules
    - Objectives of the meeting

2. Postmarketing Requirements/Postmarketing Commitments – 15 minutes
    - Applicant/Agency to provide update on status of PMR/PMC review

3. Major labeling issues – 20 minutes
    - If needed, based upon Applicant response to FDA edits.

4. Review Plans – 5 minutes

5. Wrap-up and Action Items – 5 minutes

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/s/

VIRGINIA E KWITKOWSKI
05/15/2014