DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206256

ACCELERATED APPROVAL

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 acknowledge receipt of your amendments dated February 11, 19 (2), 25, 26, and 28; March 3, 4, 5, 6, 10 (2), and 28; April 3, 4, 18, and 25; May 2 and 15; and 16 (2), 19, and 20; and July 2, 2014 (email correspondence).

This new drug application provides for the use of Beleodaq™ (belinostat) for Injection for treatment of patients with relapsed or refractory peripheral T-cell lymphoma.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled *"SPL Standard for Content of Labeling Technical Qs and As"* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels and carton and immediate container labels submitted on June 16, 2014, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 206256**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for Beleodaq™ (belinostat) for Injection was not referred to an FDA advisory committee because this drug is not the first in its class.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. You are required to conduct such studies/clinical trials with due diligence. If postmarketing studies/clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirements, as specified in your email correspondence dated July 2, 2014. These requirements, along with required completion dates, are listed below.

PMR 2178-1 Establish the optimal and 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 belinostat in combination with the CHOP regimen. Submit a complete final report with all supporting datasets.

Final Protocol Submission:	Completed
Trial Completion:	06/2015
Final Report Submission:	04/2016

PMR 2178-2 Characterize the comparative efficacy and safety of belinostat when used in combination with a treatment regimen such as CHOP, versus the combination of 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 final report with all supporting datasets.

Preliminary Protocol Submission:	07/2014
Final Protocol Submission:	12/2015
Accrual of 25% of Subjects:	04/2017
Accrual of 50% of Subjects:	04/2018
Accrual of 75% of Subjects:	04/2019
Trial Completion:	01/2020
Final Report Submission:	01/2021

Submit clinical protocols to your IND 070789 for this product. Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

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 this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of altered drug exposure from undefined drug elimination pathways which may result in higher drug exposure or metabolism to a toxic metabolite.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR 2178-3 Conduct an *in vitro* study to determine the exact contributions of UGT1A1, CYP3A4, CYP2C9, and CYP2A6 in the biotransformation of belinostat to evaluate the potential for higher drug exposure or metabolism to a potentially more toxic metabolite. Submit a complete final report with all supporting datasets.

The timetable you submitted on July 2, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/2014
Study Completion:	07/2015
Final Report Submission:	09/2015

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the unexpected serious risks of alterations in the excretion or metabolism of Beleodaq™ (belinostat) that may contribute to the occurrence of the known serious risks of fatigue, diarrhea, increased serum creatinine, thrombocytopenia and multi-organ failure observed in clinical trials, and to identify unexpected serious risks of elevated drug levels in the presence of hepatic or renal failure.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR 2178-4 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. Excretion alterations could lead to increased toxicity. Submit a complete final report with all supporting datasets.

The timetable you submitted on July 2, 2014, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	Completed
Trial Completion:	12/2014
Final Report Submission:	03/2015

PMR 2178-5 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 final report with all supporting datasets.

The timetable you submitted on July 2, 2014, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	12/2014
Trial Completion:	12/2015
Final Report Submission:	03/2016

PMR 2178-6 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 final report with all supporting datasets.

The timetable you submitted on July 2, 2014, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	12/2014
Trial Completion:	12/2015
Final Report Submission:	03/2016

PMR 2178-7 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 final report with all supporting datasets.

The timetable you submitted on July 2, 2014, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	Completed
Trial Completion:	12/2015
Final Report Submission:	03/2016

PMR 2178-8 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 final report with all supporting datasets.

The timetable you submitted on July 2, 2014, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	12/2014
Trial Completion:	12/2015
Final Report Submission:	03/2016

Submit the protocols to your IND 070789, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301)796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved package insert (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

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

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

REPORTING REQUIREMENTS

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

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

Sincerely,

{See appended electronic signature page}

Richard Pazdur, MD
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

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

/s/

RICHARD PAZDUR
07/03/2014