

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206256Orig1s000**

**OTHER REVIEW(S)**

## PMR/PMC Development Template #1

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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

PMR Description: 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 the combination of belinostat in combination with the CHOP regimen. Submit a complete study report with all supporting datasets.

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PMR Schedule Milestones:	Final Protocol Submission:	<u>Completed</u>
	Trial Completion:	<u>June 2015</u>
	Final Report Submission:	<u>April 2016</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Products that are approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled clinical trials to verify and describe clinical benefit.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Spectrum is the Sponsor of Beleodaq (belinostat) and Folutyn (pralatrexate). Folutyn was approved under the accelerated approval regulations in 2009 for the same indication as Beleodaq, for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). Since PTCL is a rare disease and to expedite the fulfillment of the PMR for both drugs, we determined that a single confirmatory trial would be the optimal way to resolve the outstanding issues, with agreement of the applicant to conduct the proposed trial and with due diligence. The safe dose of belinostat in combination with the CHOP regimen is not yet known. A phase 1 trial to establish the safe dose is needed before starting the confirmatory phase 3 trial.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Perform a phase 1 open-label, dose escalation trial in patients with PTCL to establish the dosing regimen of belinostat plus CHOP that will be used in the phase 3 trial. The primary objective is to determine the MTD of belinostat in combination with the CHOP regimen.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)  
Dose finding trial under subpart H
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- 
- Other
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5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

RCK

(signature line for BLAs)

## PMR/PMC Development Template #2

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

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

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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.

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

6. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Products that are approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled clinical trials to verify and describe clinical benefit.

7. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Spectrum is the Sponsor of Beleodaq (belinostat) and Folutyn (pralatrexate). Folutyn was approved under the accelerated approval regulations in 2009 for the same indication as Beleodaq, for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). Since PTCL is a rare disease and to expedite the fulfillment of the PMR for both drugs, we determined that a single confirmatory trial would be the optimal way to resolve the outstanding issues, with agreement of the applicant to conduct the proposed trial and with due diligence.

8. If the study/clinical trial is a **PMR**, check the applicable regulation.  
***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H/E)  
 Animal Efficacy Rule  
 Pediatric Research Equity Act  
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?  
 Assess signals of serious risk related to the use of the drug?  
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

9. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Perform a three-arm, randomized, open-label trial of belinostat+ CHOP or pralatrexate + CHOP or CHOP alone in previously untreated patients with PTCL.  
The primary endpoint is PFS using the 2007 revised Cheson IWG criteria.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)  
RCT under subpart H

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

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- Other

10. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
  
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
  - There is not enough existing information to assess these risks
  - Information cannot be gained through a different kind of investigation
  - The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
  - The trial will emphasize risk minimization for participants as the protocol is developed
- 

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

RCK

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(signature line for BLAs)

### PMR/PMC Development Template #3

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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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.

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PMR Schedule Milestones:	Final Protocol Submission:	<u>Completed</u>
	Trial Completion:	<u>December 2014</u>
	Final Report Submission:	<u>March 2015</u>

11. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Limited available data indicate belinostat is metabolized in the liver and excreted by the fecal and renal routes. However, there is no reliable data that indicates the amount of drug that is eliminating by the renal and fecal routes.

12. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

In order to properly mitigate potential safety issues and determine the need for additional studies, it is important to determine how long a drug and its metabolites stay in the body and the eventual excretion routes.

13. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
  
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
  
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

14. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A mass-balance can be conducted in few (6 to 10) patients with cancer following single dose administration.
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Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

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Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

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Other

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15. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

RCK\_\_\_\_\_

(signature line for BLAs)

## PMR/PMC Development Template #4

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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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:	<u>Completed</u>
	Trial Completion:	<u>December 2015</u>
	Final Report Submission:	<u>March 2016</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Belinostat is extensively metabolized in the liver. Increased belinostat exposures (plasma concentrations) are likely to be seen in patients with hepatic impairment. A clinical trial evaluating belinostat in patients with varying levels of hepatic impairment is currently ongoing. The final study report is required to allow for informative labeling recommendations including possible dose adjustments in patients with varying degrees of hepatic impairment.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Increased belinostat exposures are likely to be seen in patients with hepatic impairment. Increased belinostat exposure would likely result in increased toxicities such as neutropenia, thrombocytopenia, diarrhea and infections. Results of the hepatic impairment trial will allow for informative labeling recommendations including possible dose adjustments in patients with varying levels of hepatic impairment.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The trial needs to assess the pharmacokinetics and safety of belinostat in patients with mild, moderate, or severe hepatic impairment.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

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Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

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Other

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5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

RCK \_\_\_\_\_

(signature line for BLAs)

## PMR/PMC Development Template #5

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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

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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.

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PMR Schedule Milestones:	Final Protocol Submission:	<u>December 2014</u>
	Trial Completion:	<u>December 2015</u>
	Final Report Submission:	<u>March 2016</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Limited data suggest that 40% of the administered dose was excreted in urine, mostly in the form of metabolites. The renally excreted metabolite, belinostat glucuronide, is an active metabolite with cell killing activities, very high accumulation of this metabolite in patients with renal impairment may produce adverse events.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Increased belinostat glucuronide exposures are likely to be seen in patients with renal impairment. Increased belinostat glucuronide exposures would likely result in increased toxicities. Results of the renal impairment trial will allow for informative labeling recommendations including possible dose adjustments in patients with varying degrees of renal impairment.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct renal impairment trial in patients with varying degrees of renal impairment including patients with mild, moderate, severe renal function and those on chronic dialysis. Conduct the trial for sufficient duration in order to detect and assess safety and efficacy signals. Submit a complete study protocol for review and concurrence by the Agency

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials

Drug interaction or bioavailability studies or clinical trials

Dosing trials

*Continuation of Question 4*

Additional data or analysis required for a previously submitted or expected study/clinical trial  
(provide explanation)

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Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

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Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

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Other

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5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

RCK \_\_\_\_\_

(signature line for BLAs)

## PMR/PMC Development Template #6

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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

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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.

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PMR Schedule Milestones:	Final Protocol Submission:	<u>December 2014</u>
	Trial Completion:	<u>December 2015</u>
	Final Report Submission:	<u>March 2016</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Belinostat is extensively metabolized by UGT1A1. Strong UGT1A1 inhibitors are expected increase belinostat systemic exposures. Since the maximum tolerated dose of belinostat is 1000 mg/m<sup>2</sup>, factors that increase exposure to belinostat are expected to result in intolerable adverse events. In order to determine an appropriate dose of belinostat when given combination with strong UGT1A1 inhibitors, a clinical drug-drug interaction study will be required.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Increased belinostat exposures are likely when of belinostat is given concomitantly with strong UGT1A1 inhibitors. Results of the renal drug-drug interaction trial will allow for informative labeling recommendations including possible dose adjustments in patients who take belinostat concomitantly with strong UGT1A1 inhibitors.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
  
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
  
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a drug-drug interaction trial assessing the effect of strong UGT1A1 inhibitors on the pharmacokinetics of belinostat. The trial may a parallel or cross-over trial in any cancer population. Submit a complete trial protocol for review and concurrence by the Agency

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials

Dosing trials  
*Continuation of Question 4*

Additional data or analysis required for a previously submitted or expected study/clinical trial  
(provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials  
 Immunogenicity as a marker of safety  
 Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)  
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)  
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E  
 Dose-response study or clinical trial performed for effectiveness  
 Nonclinical study, not safety-related (specify)

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Other

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5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?  
 Are the objectives clear from the description of the PMR/PMC?  
 Has the applicant adequately justified the choice of schedule milestone dates?  
 Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug  
 There is not enough existing information to assess these risks  
 Information cannot be gained through a different kind of investigation  
 The trial will be appropriately designed to answer question about a drug's efficacy and safety, and  
 The trial will emphasize risk minimization for participants as the protocol is developed

---

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

RCK

(signature line for BLAs)

## PMR/PMC Development Template #7

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

---

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:	<u>December 2014</u>
	Trial Completion:	<u>December 2015</u>
	Final Report Submission:	<u>March 2016</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Belinostat is extensively metabolized by UGT1A1. UGT1A1 is a known polymorphic enzyme with allelic variants that influence enzymatic activity. A recent publication by Wang et al. (2013) indicated that subjects homozygous for UGT1A1\*28 had a 53% reduction in the production of the main metabolite (belinostat glucuronide). Since UGT1A1 metabolizes up to 90% of belinostat, patients homozygous for UGT1A1\*28 could have belinostat systemic exposures greater than those seen at doses of 1000 mg/m<sup>2</sup>. In order to determine an appropriate dose of belinostat in patients with reduced UGT1A1 activity, clinical PK and safety evaluation will be conducted in patients with wild-type, heterozygous, and homozygous UGT1A1\*28 genotypes.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Increased belinostat exposures are likely in patients with reduced UGT1A1 activity. Results of the UGT1A1 activity assessment will allow for informative labeling recommendations including possible dose adjustments in patients reduced UGT1A1 activity.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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 in order to evaluate safety following multiple dose administration. The evaluation could be part of an ongoing or future trial. Submit UGT1A1 evaluation plan for review and concurrence by the Agency

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

RCK \_\_\_\_\_

(signature line for BLAs)

## PMR/PMC Development Template #8

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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

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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.

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

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Belinostat is metabolized by multiple enzymes, including UGT1A1, CYP3A4, CYP2C9, and CYP2A6. Although UGT1A1 determine to be the primary metabolizing enzyme, the exact contribution each enzyme has not been determined. In order to determine the need for additional human drug-drug interaction trials, an in vitro study needs to be conducted in order to determine the exact contributions of each enzyme.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

In order to assess the need for additional drug-drug interaction trials, the exact contribution each enzyme needs to be determined. The liver enzymes UGT1A1, CYP3A4, CYP2C9, and CYP2A6 are reported to metabolize belinostat.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct an in vitro study to determine the contributions of liver enzymes UGT1A1, CYP3A4, CYP2C9, and CYP2A6 in the biotransformation of belinostat.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

---

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

---

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

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Other

---

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

      
RCK

(signature line for BLAs)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JESSICA L BOEHMER  
06/16/2014

ROBERT C KANE  
06/16/2014

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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CLINICAL INSPECTION SUMMARY

DATE: May 15, 2014

TO: Jessica Boehmer, M.B.A., Regulatory Project Manager  
Hyon-Zu Lee, Pharm.D., Clinical Analyst  
Virginia Kwitkowski, M.S., A.C.N.P.-B.C., Team Leader  
Division of Hematology Products (DHP)

FROM: Anthony Orenca, M.D., F.A.C.P.  
Medical Officer, GCP Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

THROUGH: Kassa Ayalew, M.D., M.P.H.  
Acting Branch Chief, GCP Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 206256

APPLICANT: Spectrum Pharmaceuticals, Inc.

DRUG: belinostat

NME: Yes

THERAPEUTIC CLASSIFICATION/REVIEW: Priority review

INDICATION: Treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL)

CONSULTATION REQUEST DATE (signed): December 17, 2013

INSPECTION SUMMARY GOAL DATE (Original):	June 8, 2014
INSPECTION SUMMARY GOAL DATE (Revised):	May 16, 2014
DIVISION ACTION GOAL DATE	August 9, 2014
PDUFA DATE:	August 9, 2014

## **I. BACKGROUND:**

Approximately one tenth of the non-Hodgkins lymphoma (NHL) group consists of the peripheral T-cell lymphoma (PTCL) subtype. PTCL comprises a heterogeneous group of predominantly nodal T-cell lymphomas, which do not have consistent immunophenotypic, genetic, or clinical features.

Belinostat is an inhibitor of histone deacetylase (HDAC) enzymes which regulate multiple cellular processes. Its inhibitory action potentially may play, in part, a role in cancer cell differentiation, growth, proliferation, migration and survival, including peripheral T-cell lymphoma. Primary treatment for most subsets of PTCL with poor prognosis, remains anthracycline-based regimens and prednisone (i.e., CHOP regimen). Most patients suffer from PTCL relapse, however there is no therapeutic management consensus.

Two domestic sites were requested for inspection for this application under Protocol PXD101-CLN-19. These clinical study sites audited had relatively high number of enrollees.

### **Protocol PXD101-CLN-19** (referred to as CLN-19 subsequently)

PXD101-CLN-19 was an open-label, multicenter, single arm efficacy and safety study, in patients with relapsed or refractory peripheral T-cell lymphoma, who had failed at least one prior systemic therapy. The primary objective of this study was to determine the objective response rate in patients with peripheral T cell lymphoma treated with belinostat monotherapy.

Patients were treated with belinostat 1000 mg/m<sup>2</sup> 30 minute IV infusion on days 1-5 every 3 weeks until there was disease progression or unmanageable treatment-related toxicities. The primary study endpoint was objective tumor response rate (ORR), defined as complete response (CR) or partial response (PR) based on independent radiology review and the modified Cheson et al. 2007 criteria.

## II. RESULTS:

Name of CI Location	Protocol/Study Site/Number of Subjects Enrolled (n)	Inspection Date	Classification*
Andrei R Shustov, M.D. Seattle Cancer Care Alliance 825 Eastlake Ave. East Mail Box G3-200 Seattle, WA 98109-1024	Protocol PXD101-CLN-19  Site #907 Subjects=7	February 11 to April 4, 2014	Preliminary: VAI
Steven M. Horwitz, M.D. Memorial Sloan-Kettering Cancer Center 1275 York Avenue New York, NY 10021	Protocol PXD101-CLN-19  Site #914 Subjects=6	Feb. 21 to 24, 2014	NAI
Sponsor: Spectrum Pharmaceuticals, Inc. 157 Technology Drive Irvine, CA 926818	Sponsor monitoring of the clinical trial, Protocol PXD101-CLN-19	March 17 to 21, 2014	Preliminary: NAI

### \*Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested = Deviations(s) from regulations. Data acceptable.

OAI = Significant deviations from regulations. Data unreliable/critical findings may affect data integrity.

Preliminary=The Establishment Inspection Report (EIR) has not been received, findings are based on preliminary communication with the field at the Office of Regulatory Affairs (ORA), or final review of the EIR is pending. Once a final letter is issued by CDER to the inspected entity and the case file is closed, the preliminary designation is converted to a final regulatory classification.

### CLINICAL STUDY SITE INVESTIGATORS

#### **1. Andrei Shustov, M.D./Protocol PXD101-CLN-19/Site #907 Seattle, WA**

##### **a. What was inspected:**

The inspection was conducted in accordance with Compliance Program 7348.811, from February 11 to April 4, 2014. A total of seven subjects were screened and enrolled. Five subjects completed the study, and had progression of disease. An audit of all the enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

**b. General observations/commentary:**

Source documents for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. The efficacy endpoints were centrally adjudicated. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection by ORA staff.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 was issued at the end of the inspection for failure to follow the study protocol according to the investigational plan and for failure to prepare and to maintain adequate records. Please see relevant examples below.

- i. Subject #907-002 died on [REDACTED] <sup>(b) (6)</sup>, but this Serious Adverse Event (SAE) was reported to the Sponsor on [REDACTED] <sup>(b) (6)</sup>, an eight day reporting delay after the event.
- ii. The effect of the new anti-cancer therapy on the End of Treatment (EOT) test results for the belinostat trial was not evaluated. Four out of five subjects (Subject #s 907-007, 907-005, 907-006 and 907-001), who survived at the end of study were administered another intravenous anti-neoplastic drug prior to the completion of the EOT procedures for the study (physical examination, ECOG performance status, hematology and coagulation panel, blood chemistry, urinalysis and ECG).
  - (a) For Subject 907-007, the EOT date was 9/15/2011. The new intravenous anti-neoplastic drug was initiated for the subject on 9/15/2011. EOT procedures (physical exam and ECOG) were performed for the subject on 10/3/2011 while the subject was already on another anti-cancer drug, pralatrexate 67 mg, for 18 days. EOT procedures (urinalysis, coagulation and ECG) were not performed.
  - (b) For Subject 907-005, the EOT date was 5/23/2011. EOT procedures were performed on 6/2/11 to 6/9/2011, 12 and 17 days after the EOT. New intravenous anti-neoplastic drug was initiated for the subject on 5/28/2011. The EOT procedures (hematology and blood chemistry) for the study drug were conducted while the subject was already on another anti-cancer drug, pralatrexate 70 mg, for 7 days. The rest of the EOT procedures (physical examination, including vital signs, ECOG performance status, urinalysis and ECG) were conducted when the subject was on pralatrexate 70 mg for 12 days.

- (c) For Subject 907-006, the EOT date was 7/4/2011. EOT procedure (ECG) was performed on 7/25/2011, 11 days after EOT. New intravenous anti-neoplastic drug was initiated for the subject on 7/18/2011. ECG was done for the study drug while the subject was already on another anti-cancer drug, pralatrexate 55 mg, for 7 days.
- (d) For Subject 907-001, the EOT was 7/26/2010. Urinalysis was done on 8/16/2010, 21 days later after the last dose of the study drug. EOT procedure (urinalysis) was conducted while the subject was already on another anti-cancer drug, pralatrexate 52 mg, for 6 days.

Medical Officer's Comment:

DHP clarified that pralatrexate was an FDA approved drug for patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). Pralatrexate may be part of the treatment regimen for "end stage" PTCL patients. Per DHP, however, none of the patients listed above had been documented as achieving a response to belinostat therapy. Therefore, the treatment with pralatrexate before or on the EOT date has no direct relevance to the NDA efficacy assessments.

The EOT procedures reported as delayed or not completed contain insufficient information to evaluate efficacy or tumor response on the basis of information provided. Additionally, there were rules (e.g., censoring) to assess tumor response, efficacy, and addressing missing data points or timing of scheduled visit assessments for this application in relation to treatment response (beyond the purview of OSI's review). DHP stated that the above citation did not have clinically significant impact on efficacy endpoint assessment for the proposed treatment.

In discussions with DHP as described above, the aforementioned regulatory deficiency observation on EOT protocol procedures were not clinically significant inspectional observations, especially where treatment efficacy determination is concerned.

- iii. Case histories with respect to observations and data pertinent to the investigation were not prepared or maintained adequately. Examples:
  - (a) Subject #907-003 withdrew consent for study drug on November 11, 2010. The previous cycle of study drug had been administered from October 11-15, 2011. The site had no record to show that the patient was monitored carefully for all adverse events until 30 days after the last study drug treatment or that efforts were made to contact the subject to assess his/her health status.
  - (b) Subject #907-004 completed his first cycle of drug treatment on December 30, 2010. A CT scan showed progressive disease on [REDACTED] (b) (6) [REDACTED]. The patient was last seen at discharge [from the hospital] on [REDACTED].

(b) (6). After termination of study treatment and during the follow-up period, there was no record in the CRF that the patient was monitored for adverse events until 30 days after his last dose of the study drug. Subsequently, the clinical study site coordinator confirmed the patient's death on (b) (6).

The List of Inspectional Observations (Form FDA 483) was communicated to the DHP Medical Team who did not consider the 483 and the above findings critical to the determination of efficacy or having an impact on subject safety.

**c. Assessment of data integrity:**

The regulatory deficiencies noted above are considered to be not critical to the determination of efficacy or impacting on subject safety. Data submitted by this clinical site appear acceptable in support of this specific indication.

**2. Steven Horwitz , M.D./Protocol PXD101-CLN-19/Site #914**

New York, New York

**a. What was inspected:**

The inspection was conducted in accordance with Compliance Program 7348.811, from February 21 to 24, 2014. A total of nine subjects were screened, and six subjects were enrolled. Six subjects completed one cycle and four of these subjects completed two cycles of treatment. An audit of the enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

**b. General observations/commentary:**

Source documents for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. The efficacy endpoints were centrally adjudicated. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection.

**c. Assessment of data integrity:**

Data submitted by this clinical site appear acceptable in support of this specific indication.

## **SPONSOR**

### **3. Spectrum Pharmaceuticals, Inc.**

Irvine, CA

#### **a. What was inspected:**

The inspection was conducted in accordance with Compliance Program 7348.810, from March 17 to 21, 2014.

The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, training of staff and site monitors.

#### **b. General observations/commentary:**

The sponsor generally maintained adequate oversight of the clinical trial. There was no evidence of under-reporting of adverse events. There were no GCP noncompliant sites reported.

A Form FDA 483 was not issued at the end of the sponsor inspection.

#### **c. Assessment of data integrity:**

The sponsor monitoring appeared reliable. Data submitted by this sponsor appear acceptable in support of the respective indication.

## **III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS**

For this open label, single arm, randomized study, two domestic sites were selected for inspection supporting this NDA: Andrei R. Shustov, M.D., and Steven M. Horwitz, M.D. The sponsor (Spectrum Pharmaceuticals, Inc.) was also inspected.

The final regulatory classification for Dr. Horwitz is NAI (No Action Indicated). The preliminary regulatory classification for Dr. Shustov is VAI (Voluntary Action Indicated). The preliminary classification for Spectrum Pharmaceuticals, Inc. is NAI (No Action Indicated). The study data collected from these clinical sites and the sponsor appear generally reliable in support of the requested indication.

*Note: The inspectional observations noted above are based on preliminary communications with the field investigator and/or preliminary review of the EIR. CDER OSI classification of inspection is finalized when written correspondence is issued to the inspected entity (e.g., principal investigator). A clinical inspection summary addendum will be generated if conclusions on the currently reported inspections change significantly, upon receipt and/or final review of the Establishment Inspection Report (EIR).*

*{See appended electronic signature page}*

Anthony Orenca, M.D.  
Medical Officer  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

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/s/  
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ANTHONY J ORENCIA  
05/16/2014

KASSA AYALEW  
05/16/2014

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy**

**PATIENT LABELING REVIEW**

Date: May 16, 2014

To: Ann Farrell, MD  
Director  
**Division of Hematology Products (DHP)**

Robert Kane, MD  
Deputy Director for Safety  
**Division of Hematology Products (DHP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Nathan Caulk, MS, BSN, RN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

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

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): BELEODAQ (belinostat)

Dosage Form and Route: for injection, for intravenous use

Application Type/Number: NDA 206-256

Applicant: Spectrum Pharmaceuticals, Inc.

## 1 INTRODUCTION

On December 9, 2013, Spectrum Pharmaceuticals, Inc. submitted for the Agency's review an original New Drug Application (NDA) 206-256 for BELEODAQ (belinostat) for injection, for intravenous use. The proposed indication for BELEODAQ (belinostat) is for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on January 31, 2014, and January 10, 2014 respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for BELEODAQ (belinostat).

The Risk Evaluation and Mitigation Strategy (REMS) is being reviewed by the Division of Risk Management (DRISK) and will be provided to DHP under separate cover.

## 2 MATERIAL REVIEWED

- Draft BELEODAQ (belinostat) for injection, for intravenous use PPI received on December 9, 2013, and received by DMPP on January 31, 2014.
- Draft BELEODAQ (belinostat) for injection, for intravenous use PPI received on December 9, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on May 6, 2014.
- Draft BELEODAQ (belinostat) for injection, for intravenous use Prescribing Information (PI) received on December 9, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on May 7, 2014.
- Draft BELEODAQ (belinostat) for injection, for intravenous use Prescribing Information (PI) received on December 9, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on May 6, 2014.
- Approved ISTODAX (romidepsin) comparator labeling dated June 13, 2013.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the PPI the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable

#### **4 CONCLUSIONS**

The PPI is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/  
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NATHAN P CAULK  
05/16/2014

JAMES S DVORSKY  
05/16/2014

BARBARA A FULLER  
05/16/2014

LASHAWN M GRIFFITHS  
05/16/2014

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** 5/12/2014

**To:** Jessica Boehmer  
Division of Hematology Products

**From:** James Dvorsky, Regulatory Reviewer  
Office of Prescription Drug Promotion

**Subject:** Beleodaq (belinostat) NDA 206256

---

We acknowledge receipt of your January 10, 2014, consult request for the proposed product labeling (Package Insert (PI)) for NDA 206256. We have reviewed the revised draft PI for Beleodaq and offer the following comments below. Note that this review was based upon the May 6, 2014 version of the label.

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/s/  
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JAMES S DVORSKY  
05/12/2014



# Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: April 7, 2014

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.  
Division Director  
Division of Cardiovascular and Renal Products /CDER

To: Jessica Boehmer  
DHP

Subject: QT-IRT Consult to NDA206256

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated Jan 17, 2014 regarding the Integrated Summary of Cardiac Safety submitted by the sponsor as part of their NDA application. The QT-IRT received and reviewed the following materials:

- Your consult
- Integrated Summary of Cardiac Safety
- Annotated draft labeling
- Investigator's Brochure
- QT-IRT previous reviews for IND70789 (2008/06/09 and 2011/03/14)

## QT-IRT Comments for (division)

Based on information available, QT prolongation with belinostat cannot be confirmed or excluded. However, large QT prolongation (e.g., > 20 ms) with belinostat seems unlikely.

### BACKGROUND

Belinostat (PXD101) is a pan inhibitor of histone deacetylase (HDAC) enzymes, which alters acetylation levels of histone and non-histone proteins, thus influencing chromatin accessibility and ultimately gene transcription.

Preclinical experience showed that no significant risk of QT prolongation based on in vitro biological findings from the hERG (IC<sub>20</sub> of 270 μM) or Purkinje fiber study.

In the current NDA submission, belinostat is indicated for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). The proposed dose of belinostat is 1000 mg/m<sup>2</sup> administered over 30 minutes by intravenous (IV) infusion on Days 1-5 of a 21-day cycle. Cycles can be repeated every 21 days until disease progression or unacceptable toxicity. In this integrated cardiac safety report, an effect-exposure analysis of the potential effect of belinostat on cardiac repolarization from 8 clinical studies (N=380), and analyses of ECG information across the 13 clinical studies (N=529) were submitted.

A linear mixed effects modeling approach was used to quantify the relationship between the plasma concentration of belinostat and the change from Baseline in QTc intervals. At 0 belinostat concentration, the intercept showed about a 10 ms change in QTcF from pre-treatment Baseline, probably representing background spontaneous variability in QTc changes over time. Using all interpretable paired data, the slope of the effect-exposure relationship was flat, demonstrating that there was no signal of any meaningful effect of belinostat on cardiac repolarization whether using C<sub>max</sub> or C<sub>min</sub> or by viewing belinostat therapy alone or in combination with other agents (see the following table and figure). At the predicted C<sub>max</sub> of 35697.57 ng/mL (defined in the Report Methods Section), the current model predicts a change from Baseline in QTcF of 7.6 ms with an upper confidence interval of 9 ms. Taking the 10 ms background change in QTc predicted by the model into consideration, belinostat peak blood concentrations are unlikely to be associated with clinically relevant QTc changes.

**Table 3**  $\Delta$ QTc versus the Belinostat Plasma Concentration- Estimates from Linear Mixed Model [1]

QTc Fridericia, and QTc Bazett (msec)				
QT Parameter	Slope of Plasma Conc. Effect on $\Delta$ QTc [1]	Standard Error of Slope of Plasma Conc. Effect on $\Delta$ QTc [1]	p-value Slope of Plasma Conc. Effect on $\Delta$ QTc [1]	Overall Model Fit (p-value) [1]
QTcF	0.00000199	0.00001405	0.8872	<0.0001
QTcB	-0.00000067	0.00001578	0.9663	<0.0001

QT Parameter	Mean Cmax		Mean Cmin	
	Predicted $\Delta$ QTc at Average Cmax 35697.57 ng/mL	One-sided Upper 95% Confidence Bound of Predicted $\Delta$ QTc [2]	Predicted $\Delta$ QTc at Average Cmax 11.29 ng/mL	One-sided Upper 95% Confidence Bound of Predicted $\Delta$ QTc [2]
QTcF	7.572	8.948	7.501	8.731
QTcB	10.011	11.558	10.035	11.419

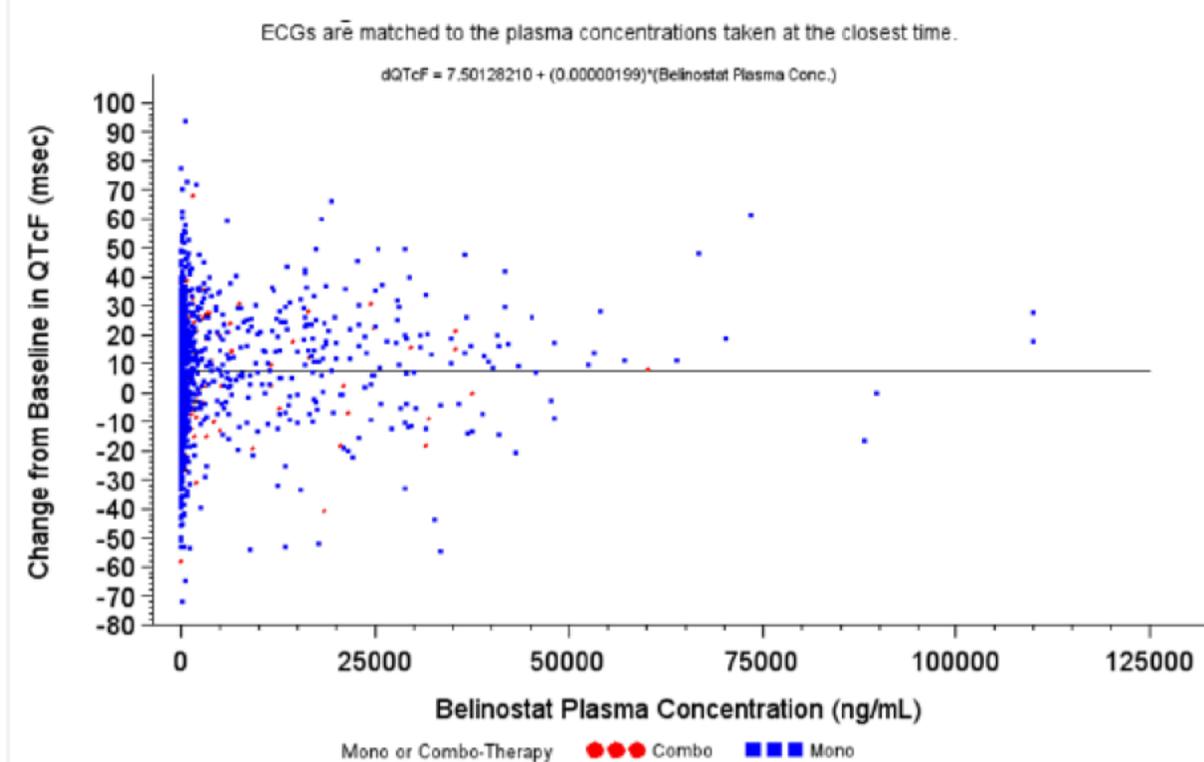
[1] Linear mixed effects model is fit for change from baseline (ie, subtracted) versus the plasma concentration. Intercept is included in the model as a random effects term; models with concentration as a random effects term do not converge. Mean ECGs were matched to the closest plasma concentration to the mean time of the ECG, using the matching technique within each study. Model covariance structure is a unstructured for both QTcF and QTcB models.

2] Upper Bound = upper one-sided 95% linear mixed model based confidence limit.

Mean Cmax and mean Cmin were provided by the Sponsor.

Source: The sponsor's Integrated Summary of Cardiac Safety, Page 73

**Figure 1: Belinostat Plasma Concentration Versus Change from Baseline in QTcF Duration**



Source: The sponsor's Integrated Summary of Cardiac Safety, Page 74

Thus, in conclusion, there was no clear signal that belinostat caused cardiac events in mono or combination therapy, nor does belinostat have any clear effects on ECG parameters irrespective of the route of administration (IV infusion, PO or as CIV infusion). Based on the data collected, if belinostat does have any effect on the duration of the QTc interval, the likelihood is that any such effect would be less than 10 ms and hence would be of little clinical relevance in the target population.

QT-IRT reviewer's comments: *The sponsor's exposure-response analysis showed that there is no direct relationship between plasma belinostat concentrations and dQTcF because the slope of the relationship was not statistically significant. However, the intercept (~10 ms) is significant. The sponsor is arguing that the significant intercept is due to background spontaneous variability in QTc changes over time which is not drug-related. However, there are various drug-related reasons may cause a significant intercept and a non-significant slope in the pooled analysis. For example:*

- 1. QT prolongation stem from metabolites of belinostat. Belinostat plasma levels declined rapidly following administration to sub-pharmacological concentrations with an elimination half-life of ~ 1 h. However, belinostat metabolites could be detected up to one week in plasma and excreta after a single dose oral and IV administration. If the metabolites cause QT prolongation, it may explain the observed 10-ms change in QTcF from baseline at 0 belinostat concentration.*
- 2. There may be a hysteresis between plasma belinostat concentrations and QTc prolongation (e.g., other off-target actions). One such mechanism might be block of hERG trafficking, but this would likely lead to progressive increases in QT over time.*

*Meanwhile, there are two other major limitations in the sponsor's exposure-response analysis dataset:*

- 1. The matched PK samples were not collected at the time of ECG recording. Because of the relative short half-life, a substantial difference in belinostat concentration level is expected (and was observed) even for a short time deviation.*
- 2. The QT effect had not been monitored at the peak belinostat concentrations occur immediately after dosing. At the predicted C<sub>max</sub> of mg/mL or higher, the observed information is very limited compared to the lower concentrations.*

Events suggestive of proarrhythmia were not seen.

ECGs were reviewed in the ECG Warehouse. These ECGs are not of particularly high quality, but the sponsor's analyses of QT appear to be reasonable and unbiased.

We suggest the following slight edits to the sponsor's proposed labeling in section 12.3:

#### ***Cardiac Electrophysiology***

Multiple clinical trials have been conducted with Beleodaq, in many of which ECG data were collected and analyzed by a central laboratory. Analysis of clinical ECG and belinostat plasma concentration data

demonstrated no (b) (4)-meaningful effect of Beleodaq on cardiac repolarization.

None of the trials showed any clinically relevant changes caused by Beleodaq on heart rate, PR duration or QRS duration as measures of autonomic state, atrio-ventricular conduction or depolarization; there were no cases of Torsades de Pointes.

Thank you for requesting our input into the development of this product under NDA206256. We welcome more discussion with you now and in the future. Please feel free to contact us via email at [cdcrpqt@fda.hhs.gov](mailto:cdcrpqt@fda.hhs.gov)

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/s/  
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JIANG LIU  
04/07/2014

NORMAN L STOCKBRIDGE  
04/08/2014

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## **LABEL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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<b>Date of This Review:</b>	March 31, 2014
<b>Requesting Office or Division:</b>	Division of Hematology Products (DHP)
<b>Application Type and Number:</b>	NDA 206256
<b>Date of Submission:</b>	December 06, 2013
<b>Product Name and Strength:</b>	Beleodaq (Belinostat) for Injection, 500 mg/vial
<b>Product Type:</b>	Single Ingredient
<b>Rx or OTC:</b>	Rx
<b>Applicant/Sponsor Name:</b>	Spectrum Pharmaceuticals, Inc.
<b>OSE RCM #:</b>	2014-12
<b>DMEPA Primary Reviewer:</b>	Michelle Rutledge, PharmD
<b>DMEPA Team Leader:</b>	Yelena Maslov, PharmD

---

### 1. REASON FOR REVIEW

This review evaluates the proposed prescribing information, container label and carton labeling for Beleodaq for areas of vulnerability that could lead to medication errors.

### 2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Table 1. Materials Considered for this Label and Labeling Review</b>	
<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
FAERS	B - N/A
ISMP Newsletters	C
Previous DMEPA Reviews	D
Human Factors Study (if applicable)	E - N/A
Other (if applicable)	F - N/A
Container Label, Carton Labeling, and Instructions for Use or Medication Guide (if applicable)	G

N/A = not applicable for this review

### 3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the label and labeling, and identified the following areas of vulnerability to error:

- The use of symbols, abbreviations, and large doses without properly placed commas in the prescribing information.
- The omission of the duration of administration (i.e., Intravenous Infusion), product strength per vial, and “Discard Unused Portion” statement on the carton and container labels.
- The close proximity and prominence of the Rx only statement on the principal display panel.

Thus, recommendations on increasing readability and prominence of important information on the proposed labels and labeling will be made in Section 4.

### 4. CONCLUSION & RECOMMENDATIONS

We conclude that the proposed labels and labeling can be improved to increase readability, increase prominence of important safety information, and to provide clarity in the Dosing and Administration section of the prescribing information.

## RECOMMENDATIONS FOR THE APPLICANT

### A. Prescribing Information

1. The prescribing information includes the use of error-prone symbols<sup>1</sup>. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations<sup>1</sup> appear throughout the package insert. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products. Therefore, please revise accordingly, for example, to read "greater than and equal to" instead of the use of symbols ( $\geq$ ) and read "intravenous" instead of the use of the IV abbreviation.
2. ISMP has identified using commas for dosing units at or above 1,000 mg improves readability<sup>1</sup>. Therefore, please add a comma when the 1,000 mg dose is designated to read, "1,000 mg".
3. We note the use of the abbreviations (e.g. NCI-CTCAE) in the dosage and administration sections of the prescribing information. We recommend for the Applicant to provide the intended meaning of those abbreviations prior to their use to prevent misinterpretations and confusion (e.g. The National Cancer Institute-Common Terminology Criteria for Adverse Events).

### B. Carton and Container Labels

1. Revise the product strength statement to "500 mg per vial" which is the customary format for injectable products that require reconstitution<sup>2</sup>.
2. Revise the route of administration statement to "For Intravenous Infusion Only" to help ensure the correct use of the drug.
3. The vial is meant as a single dose product, therefore revise the single use statement to read "Single-Use Vial. Discard Unused Portion".
4. 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 panel<sup>2</sup>.

---

<sup>1</sup> ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2013 [cited 2014 March 31]. Available from: <http://www.ismp.org/tools/errorproneabbreviations.pdf>.

<sup>2</sup> Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Draft Guidance [Internet]. FDA. April 2013 [cited 2014 March 31]. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Beleodaq that Spectrum Pharmaceuticals, Inc. submitted on December 6, 2013.

Table 2. Relevant Product Information for [Beleodaq]	
Active Ingredient	Belinostat
Indication	Treatment of patients with relapsed or refractory peripheral T-cell lymphoma(PTCL)
Route of Administration	Intravenous infusion
Dosage Form	Lyophilized powder for injection
Strength	500 mg per vial (50 mg/mL when reconstituted)
Dose and Frequency	1,000 mg mg/m <sup>2</sup> administered over 30 minutes on days 1 to 5 on a 21-day cycle
How Supplied	30 mL clear vial
Storage	Store at 25°C in outer carton until use. Excursions are permitted for 15°C - 30°C (59° - 86°F)

### APPENDIX C. ISMP NEWSLETTERS

#### C.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on March 31, 2014 using the search terms listed below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
Date Range	March 31, 2014
ISMP Newsletter Search Strategy	Match Any of the words
Search Terms	Beleodaq, Belinostat

#### C.2 Results

Our search of ISMP did not yield any articles.

## **APPENDIX D. PREVIOUS DMEPA REVIEWS**

### **D.1 Methods**

We searched the [L:Drive] using the terms, Beleodaq to identify reviews previously performed by DMEPA.

### **D.2 Results**

DMEPA has reviewed Beleodaq Proprietary Name Review information in the following OSE reviews:

2014-16986, dated February 25, 2014

2013-1967, dated November 4, 2013

## **APPENDIX G. CONTAINER LABEL, CARTON LABELING, INSTRUCTIONS FOR USE, MEDICATION GUIDE**

### **G.1 List of Label and Labeling Reviewed**

We reviewed the most recent Beleodaq labels and labeling submitted by Spectrum Pharmaceuticals, Inc. on December 6, 2013.

- Container label
- Carton label
- Prescribing Information (not listed)

### **G.2 Label and Labeling Images**





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MICHELLE K RUTLEDGE  
04/03/2014

YELENA L MASLOV  
04/03/2014

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 206256 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Beleodaq <sup>TM</sup> for Injection Established/Proper Name: belinostat Dosage Form: intravenous (IV) infusion Strengths: 500 mg/vial		
Applicant: Spectrum Pharmaceuticals, Inc. Agent for Applicant (if applicable):		
Date of Application: December 8, 2013 Date of Receipt: December 9, 2013 Date clock started after UN:		
PDUFA Goal Date: August 9, 2014		Action Goal Date (if different):
Filing Date: February 7, 2014		Date of Filing Meeting: January 23, 2014
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): Belinostat is indicated for the treatment of patients with relapsed or refractory peripheral T-Cell lymphoma (PTCL).		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> .		
Review Classification:  <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>  <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input checked="" type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division ( <i>if OTC product</i> ):				
List referenced IND Number(s): 070789				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Add proprietary name in DARRTS
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>	<input type="checkbox"/>	<input type="checkbox"/>		
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid  <input checked="" type="checkbox"/> Exempt (orphan, government)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2)</b>  <b>(NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1482 1349 1619"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																		

<b>Designations and Approvals list at:</b> <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>				
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ( <i>NDAs/NDA efficacy supplements only</i> )  <b>If yes, # years requested:</b>  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use ( <i>NDAs only</i> )?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>If yes</b> , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ( <i>Original 351(a)BLAs/BLA supplements only</i> )  <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i>  <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement if exclusivity has not yet been granted. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

<b>Format and Content</b>	
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)
<b>If mixed (paper/electronic) submission</b> , which parts of the application are submitted in electronic format?	

<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission, does it follow the eCTD guidance?</b> <sup>1</sup> <b>If not, explain (e.g., waiver granted).</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Index:</b> Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:  <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)  <b>If no, explain.</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?  <b>If yes, BLA #</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?  <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<p>included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b><u>PREA</u></b> Does the application trigger PREA?  <i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Orphan Drug Designation
<b>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</b>  <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</b>  <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b><u>BPCA</u> (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b><u>Proprietary Name</u></b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b><u>REMS</u></b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	A Risk Management Plan is submitted, but it is not a true REMS
<b><u>Prescription Labeling</u></b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in PLR format? <sup>4</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send <i>WORD</i> version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	QT-IRT
<i>If yes, specify consult(s) and date(s) sent:</i>				
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b> December 10, 2009 – CMC November 29, 2007 - Clinical	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> May 29, 2013	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> September 4, 2008	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** January 23, 2014

**BLA/NDA/Supp #:** 206256

**PROPRIETARY NAME:** Beleodaq™ for Injection

**ESTABLISHED/PROPER NAME:** belinostat

**DOSAGE FORM/STRENGTH:** 500 mg per vial, lyophilized [intravenous formulation]

**APPLICANT:** Spectrum Pharmaceuticals

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** Treatment of Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma

**BACKGROUND:**

Spectrum is pursuing Accelerated Approval for Beleodaq™, a pan-histone deacetylase (HDAC) inhibitor, for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). The study that serves as the primary basis of safety and efficacy for this NDA is PXD101-CLN-19 (CLN-19): “A Multicenter, Open-Label Trial of Belinostat in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma.” Under the Special Protocol Assessment (SPA) process, the FDA agreed on September 4, 2008 that the design and planned analyses of CLN-19, with a primary efficacy endpoint of objective response rate, were adequate to address the objectives necessary to support a regulatory submission.

Supportive safety data from other belinostat monotherapy and combination therapy studies in various tumor types are also included in this original NDA as agreed during the pre-NDA meeting on May 29, 2013.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jessica Boehmer	Y
	CPMS/TL:	Ebla Ali Ibrahim Lara Akinsanya (Acting)	N Y
Cross-Discipline Team Leader (CDTL)	Virginia Kwitkowski		Y
Clinical	Reviewer:	Hyon-Zu Lee	Y (phone)
	TL:	Virginia Kwitkowski	Y

Clinical Pharmacology	Reviewer:	Bahru Habtemariam	N
	TL:	Julie Bullock	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Stacey Ricci Pedro Del Valle	Y Y
	TL:	Haleh Saber	Y
Statistics	Reviewer:	Erik Bloomquist	Y
	TL:	Yuan-Li Shen	Y
Product Quality (CMC)	Reviewer:	Xiao-Hong Chen Minerva Hughes (Biopharm)	Y Y
	TL:	Janice Brown/Ali Al Hakim Angelica Dorantes (Biopharm)	Y/N N
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:	Neal Sweeney	Y
	TL:		
CMC Labeling Review	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:	Vipul Dholokia	N
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Michelle Rutledge	Y
	TL:	Yelena Maslov	Y (phone)
OSE/DRISK (REMS)	Reviewer:		
	TL:	Cynthia LaCivita	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Anthony Orenca	Y
	TL:	Janice Pohlman	N
Other reviewers	James Dvorsky, OPDP Sonny Saini, OSE RPM Tracy Salaam, DPV TL Wana Manitsitkul, DPV SE Joyce Weaver, DRISK		Y Y (phone) Y Y Y
Other attendees	Richard Pazdur, OHOP Office Director Ann Farrell, DHP Division Director Edvardas Kaminskas, DHP Deputy Dir. Janet Higgins, DHP RPM Amy Chi, DHP RPM Tinya Sensie, DHP RPM		

**FILING MEETING DISCUSSION:**

<b>GENERAL</b>	
<ul style="list-style-type: none"> <li>• 505(b)(2) filing issues: <ul style="list-style-type: none"> <li>○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> <p>Describe the scientific bridge (e.g., BA/BE studies):</p> </li> </ul>	<input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable
<b>CLINICAL</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
<p><b>Comments:</b> 1 Clinical Comment, 1 Information Request for the letter</p>	<input checked="" type="checkbox"/> Review issues for 74-day letter

<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input checked="" type="checkbox"/> To be determined  Reason:
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIostatistics</b></p>	<input type="checkbox"/> Not Applicable

<p><b>Comments:</b> 1 Information Request for the letter</p>	<input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b> There may be a particulate issue, they will know more by midcycle. No comment for the letter at this time.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?   <b>If no</b>, was a complete EA submitted?   <b>If EA submitted</b>, consulted to EA officer (OPS)?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul>	<p><input type="checkbox"/> N/A</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	<p>None</p>
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>

<ul style="list-style-type: none"> <li>Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>REGULATORY PROJECT MANAGEMENT</b>	
<p><b>Signatory Authority:</b> Richard Pazdur, Director, OHOP</p> <p><b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): March 7, 2014</p> <p><b>21<sup>st</sup> Century Review Milestones: MCC: March 17, 2014, PDUFA Goal Date: August 9, 2014</b></p> <p><b>Comments:</b></p>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input type="checkbox"/> No review issues have been identified for the 74-day letter.  <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): 1 Clinical Comments, 1 Clinical IR, 1 Stats IR  <u>Review Classification:</u>  <input type="checkbox"/> Standard Review  <input checked="" type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> </ul>

	<ul style="list-style-type: none"> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at:  <a href="http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f">http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f</a> ]</p>
<input type="checkbox"/>	Other

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/s/  
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JESSICA L BOEHMER  
02/04/2014

MONSURAT O AKINSANYA  
02/04/2014

**REGULATORY PROJECT MANAGER  
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW  
OF THE PRESCRIBING INFORMATION**

**Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements**

**Application:** NDA 206256

**Application Type:** NME NDA

**Name of Drug/Dosage Form:** BELEODAQ™ (belinostat) FOR INJECTION

**Applicant:** Spectrum Pharmaceuticals, Inc.

**Receipt Date:** December 9, 2013

**Goal Date:** August 9, 2014

## **1. Regulatory History and Applicant's Main Proposals**

Spectrum is pursuing Accelerated Approval for Beleodaq™, a pan-histone deacetylase (HDAC) inhibitor, for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). The study that serves as the primary basis of safety and efficacy for this NDA is PXD101-CLN-19 (CLN-19): "*A Multicenter, Open-Label Trial of Belinostat in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma.*" Under the Special Protocol Assessment (SPA) process, the FDA agreed on September 4, 2008 that the design and planned analyses of CLN-19, with a primary efficacy endpoint of objective response rate, were adequate to address the objectives necessary to support a regulatory submission.

Supportive safety data from other belinostat monotherapy and combination therapy studies in various tumor types are also included in this original NDA as agreed during the pre-NDA meeting on May 29, 2013.

## **2. Review of the Prescribing Information**

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

## **3. Conclusions/Recommendations**

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix. All SRPI format deficiencies of the PI will be conveyed to the applicant in the Filing Letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by February 14, 2014. The resubmitted PI will be used for further labeling review.

# Selected Requirements of Prescribing Information

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## Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

## Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

### HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

**Comment:**

- YES** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

**Instructions to complete this item:** If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

**Comment:**

- NO** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

**Comment:** *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.*

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

**Comment:**

## Selected Requirements of Prescribing Information

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

*Comment:*

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

*Comment:*

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a BOXED WARNING is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state "None.")
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

*Comment:*

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

*Comment:*

#### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

*Comment:*

#### Product Title in Highlights

## Selected Requirements of Prescribing Information

- YES** 10. Product title must be **bolded**.

Comment:

### Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

### Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

### Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

### Indications and Usage in Highlights

**YES**

## Selected Requirements of Prescribing Information

19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

### Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

### Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

### Adverse Reactions in Highlights

- NO** 22. For drug products other than vaccines, the 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**”.

Comment: *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.*

### Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

### Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.  
***Comment:***
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.  
***Comment:***
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.  
***Comment:***
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
***Comment:***
- NO** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].  
***Comment:*** *In the Table of Contents, all subsection headings must be indented.*
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
***Comment:***
- NO** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”  
***Comment:*** *Correct the statement at the end of the Table of Contents to read: “\*Sections or subsections omitted from the full prescribing information are not listed.”*

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- NO** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

## Selected Requirements of Prescribing Information

***Comment:*** 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)]” or “[see Warnings and Precautions (5.2)]”.

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

***Comment:***

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

***Comment:***

#### BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

***Comment:***

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

***Comment:***

#### CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

***Comment:***

#### ADVERSE REACTIONS Section in the FPI

- N/A** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

***Comment:***

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

***Comment:***

## Selected Requirements of Prescribing Information

### PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

**Comment:**

- NO** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

**Comment:** *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.*

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/s/  
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JESSICA L BOEHMER  
02/04/2014

MONSURAT O AKINSANYA  
02/04/2014