CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206256Orig1s000

CHEMISTRY REVIEW(S)

NDA 206-256

Beleodaq (belinostat) for Injection, 500 mg

Spectrum Pharmaceuticals, Inc.

Xiao-Hong Chen, Ph.D.

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I

CMC Review of NDA 206-256

For the Division of Hematology Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 206-256

2. REVIEW #1:

3. REVIEW DATE: 28-APR-2014

4. REVIEWER: Xiao-Hong Chen, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA submission	08-Dec-2013
Amendment SN006	28-Feb-2014
Amendment SN0013	28-Mar-2014
Amendment SN0015	04-Apr-2014
Amendment SN0017	25-Apr-2014

7. NAME & ADDRESS OF APPLICANT:

NAME:	Spectrum Pharmaceuticals, Inc.
ADDRESS:	157 Technology Drive Irvine, CA 92618
REPRESENTATIVE:	N/A.
TELEPHONE:	(720) 540-5343

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Beleodaq®
b) Non-Proprietary Name (USAN): belinostat

c) Code Name/#
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: P

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

10. PHARMACOL. CATEGORY: Treatment of Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma

11. DOSAGE FORM: Lyophilized powder for Injection

12. STRENGTH/POTENCY: 500 mg

13. ROUTE OF ADMINISTRATION: IV

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

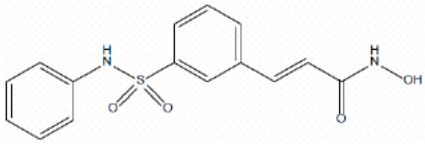
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

____SPOTS product – Form Completed

_X__Not a SPOTS product

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

Name (USAN, INN): belinostat
Name (CAS): 2-Propenamide, *N*-hydroxy-3-[3-[(phenylamino)sulfonyl]phenyl]-, (2*E*)-
IUPAC Name: (2E)-3-[3-(anilinosulfonyl)phenyl]-N-hydroxyacrylamide
Other Name: *N*-hydroxy-3-(3-phenylsulphamoylphenyl) acrylamide
Company code: PXD101
(CAS) Registry Number: 414864-00-9, 866323-14-0
Mol. Formula: $C_{15}H_{14}N_2O_4$ S
Mol. Wt.: 318.35 g/mole
Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENT
26926	II	Spectrum Pharmaceuticals, Inc. 157 Technology Drive Irvine, CA 92618	Belinostat DS	1	**Adequate**	4-23-2014	DMF holder is also the applicant of the NDA.
(b) (4)	III	(b) (4)		4	**Adequate**	4-2-2014	
	III			3	**Adequate**	21-May-2011	Reviewed Josephine Jee.
	III			7	**Reviewed by microbiologist.**	8-2-2013	DMF describes (b) (4). Reviewed by micro team.

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Supporting Documents: None

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	70789	Spectrum Pharmaceuticals, Inc.	Original IND submitted on 16-Dec-2004.

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	25-Feb-2014	Office of Compliance
Biopharmaceutics	Pending		Minerva Hughes, Ph.D. Note that Beleodaq (belinostat) for Injection is an IV injection product. Per my discussion with Dr. Hughes, there is no outstanding issue with this NDA.
Proprietary Name	Acceptable	28-Feb-2014	Tingting N Gao, PharmD. and Yelena L Maslov, PharmD.
Methods Validation	Pending	24-Jan-2014	A methods validation request was sent on 24-Jan-2014 and the results are pending. It should be noted that the approvability of the NDA is not dependent upon the results.
EA (Categorical exclusion)	Acceptable	25-Apr-2014	Xiao Hong Chen, Ph.D.
Microbiology	Acceptable	9-JUL-2013	Neal Sweeney, Ph.D.

The Chemistry Review for NDA 206-256

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC perspective, this application is recommended for Approval. EES has an overall "Acceptable" recommendation for this NDA.

Review of the package insert labeling and container/carton labels is under way. The following comment should be included in the action letter:

An expiration dating period of 24-months is granted for Beleodaq(belinostat) for Injection when stored at 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (between 59°F and 86°F).

B. Recommendation on Post Marketing Requirements, Post Marketing Commitments, Agreements, and/or Risk Management Steps, if Approvable.

N/A.

II. Summary of Chemistry Assessments

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

Drug Product

Belinostat for Injection is supplied as a sterile, yellow lyophilized (b) (4) The drug product contains belinostat (drug substance), 500 mg/vial, (b) (4) L-Arginine, 1000 mg/vial. (b) (4) All excipients comply with USP compendial standards.

The product is supplied in a 30 mL Type I clear glass vial closed with a (b) (4)-coated (b) (4) stopper. The vial is capped with an aluminum 'flip-off' seal. The primary container is enclosed in a carton. As indicated in the proposed labeling, the product is reconstituted in 9 mL Sterile Water for Injection. Prior to administration, the reconstituted belinostat (50 mg/mL) is admixed with 0.9% saline to the desired strength for infusion.

The pivotal clinical study was conducted using a (b) (4) formulation, Belinostat Injection (50 mg/mL). (b) (4), a lyophilized form of belinostat was developed as the commercial product. The lyophilized formulation, Belinostat for Injection (500 mg/vial), after reconstitution with 9 mL Sterile Water for Injection, is qualitatively and quantitatively identical to the (b) (4) formulation.

Three registration stability batches have been manufactured at (b) (4) representing (b) (4) of the proposed commercial scale, which is (b) (4) Clinical supplies have also been manufactured at a scale of (b) (4) per batch by (b) (4) The knowledge gained from manufacturing over 20 batches (16 clinical batches and 7 registration batches) with the impurity profile that meet the ICH guidance forms the basis for the commercial process.

Stability studies conducted under the ICH Long-term (25°C/60% RH), intermediate (30°C/65% RH) and accelerated (40°C/75% RH) storage conditions demonstrated that the drug product is very stable under the intended storage conditions, i.e. *20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (between 59°F and 86°F).* The proposed 24 month shelf life is deemed acceptable.

Incompatibility was initially observed for the drug product diluted in saline, which showed that the level of particulate matter exceeds the USP<788> requirement for large parenteral products. In response to Agency's information request regarding particulates observed in the Belinostat diluted in 0.9% Sodium Chloride Injection in either (b) (4), the applicant carried out the multi-variable study to evaluate drug admixture conditions that would yield solutions that meet the USP <788> particulate matter specification. The results of these studies show that all samples met the USP <788> particulate matter specification through the (b) (4) hold time of the admixture solutions. The applicant recommends the use of an in-line 0.22 micron filter for administration as an additional safety measure.

Drug Substance

The drug substance is belinostat. The chemical name is 2-Propenamide, *N*-hydroxy-3-[3-[(phenylamino)sulfonyl]phenyl]-, (2*E*)-. It has a molecular formula of $C_{15}H_{14}N_2O_4S$ and it has a molecular weight is 318.35.

Complete CMC information has been submitted in the Type 2 DMF #026926. The DMF that was referenced by the applicant has been reviewed and was found to be adequate. Refer to the review conducted by this reviewer dated Apr. 23, 2014.

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

Beleodaq® is administered by intravenous infusion at the dose of 1000 mg/m^2 daily using an infusion set with an in-line filter. Prior to IV infusion, the drug product is reconstituted with 9 mL of sterile water for injection followed by dilution in 250 mL of 0.9% sterile saline solution.

C. Basis for Approvability Recommendation

From a CMC perspective, Spectrum Pharmaceuticals, Inc. has submitted sufficient CMC information to support the approval of the drug. Spectrum Pharmaceuticals has adequately addressed the CMC comments/deficiencies identified in the review. There are no outstanding deficiencies with the application. The referenced Type II DMF #26926 for the belinostat drug substance has been reviewed and is found to be adequate to support the NDA. An overall

"Acceptable" recommendation was made by the Office of Compliance for the pre-approval inspection of the NDA.

III. Administrative

A. Reviewer's Signature

See appended electronic signature page.

B. Endorsement Block

Reviewer Name/Date: Xiao-Hong Chen, Ph.D.
Branch Chief Name/Date: Ali Al Hakim, Ph.D.

C. CC Block

Jessica Boehmer/OHOP/DHP/Regulatory PM
Janice Brown/ONDQA/CMC Lead
Jewell Martin/ONDQA/PM
Ali Al Hakim/ONDQA/DNDQA I/Branch Chief
Ramesh Sood/ONDQA/DNDQA I Acting Director

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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.

/s/

XIAO H CHEN
05/02/2014

JANICE T BROWN
05/07/2014
Janice Brown for Ali Al Hakim

ONDQA Initial Quality Assessment (IQA) and Filing Review
CMC and Biopharmaceutics
NDA 206256, Belinostat for Injection, Spectrum Pharmaceuticals, Inc.

IQA and Filing Review Cover Sheet

1. **NEW DRUG APPLICATION NUMBER:** 206256

2. **DATES AND GOALS:**

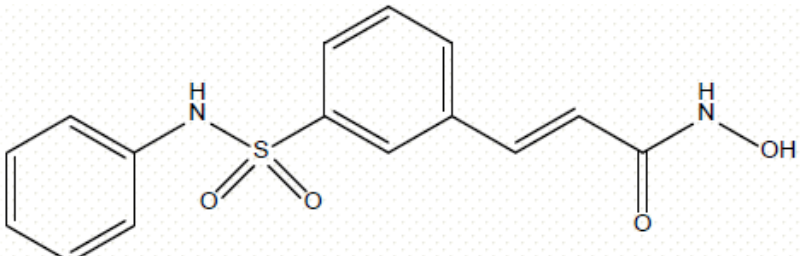
Letter Date: 08-Dec-2013	Submission Received Date: 08-Dec-2013
PDUFA Goal Date: 09-Aug-2014 (Priority)	

3. **PRODUCT PROPERTIES:**

Trade or Proprietary Name:	Beleodaq
Established or Non-Proprietary Name (USAN):	Belinostat
Dosage Form:	Injection, Powder, Lyophilized, for Solution
Route of Administration	Intravenous
Strength/Potency	500 mg/mL
Rx/OTC Dispensed:	Rx

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

5. **DRUG SUBSTANCE STRUCTURAL FORMULA:**



Molecular formula: $C_{15}H_{14}N_2O_4S$
Molecular Weight: 318.35 g/mole

6. **NAME OF APPLICANT (as indicated on Form 356h):**

Spectrum Pharmaceuticals, Inc.

7. SUBMISSION PROPERTIES:

Review Priority:	Priority
Submission Classification (Chemical Classification Code):	Type 1 – New Molecular Entity
Application Type:	505(b)(1)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	DHP

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	
Clinical Pharmacology		X	
Establishment Evaluation Request (EER)	X		Entered on 16-Dec-2013
Pharmacology/Toxicology			Determined by primary reviewer
Methods Validation	X		Consult submitted on 27-Jan-2014
Environmental Assessment	X		A claim of categorical exclusion from the requirement to submit an Environmental Assessment (EA) was requested
CDRH		X	
Other			N.A.

9. QUALITY REVIEW TEAM:

Discipline	Reviewer
CMC	Xiao-Hong Chen, Ph.D.
Biopharmaceutics	Minerva Hughes, Ph.D.
Microbiology	Neal Sweeney, Ph.D.
Facilities	Vipul Dholakia, Ph.D.

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective? Yes
CMC Filing Issues: None

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter? No
CMC Comments for 74-Day Letter: None

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective? Yes
Biopharmaceutics Filing Issues:
1. None

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter? No
Biopharmaceutics Comments for 74-Day Letter:
1. None

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective? Yes
Microbiology Filing Issues: See Microbiology Filing Review for details and for any potential Microbiology review issues.

Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
No	No	No	

Is a team review recommended?	Yes
Suggested expertise for team:	
CMC Reviewer: Xiao-Hong Chen, Ph.D.	
Biopharmaceutics Reviewer: Minerva Hughes, Ph.D.	
Product Quality Microbiology Reviewer: Neal Sweeney, Ph.D.	
Facilities Reviewer: Vipul Dholakia, Ph.D.	

CMC Summary of Critical Issues and Complexities

1. Drug Substance:

- (b) (4)

2. *Drug Product*

- (b) (4)

- (b) (4)

- The study assessing compatibility of the admixture solution with infusion bags was carried out using reconstituted drug product. Insignificant changes were observed in

appearance, assay, impurities, and pH; however, particulates were observed, indicating physical incompatibility of drug formulation with saline and/or (b) (4). The admixed solution was found to be stable over the duration of the study (72 hours). However, particulates above the limit established in the USP <788> for large volume parenterals were observed. The particulate level was reduced to an acceptable level with use of 0.22 micron in-line filter. In line filter is recommended in the proposed labeling. Suggest discussing with the applicant the source of the incompatibility.

Biopharmaceutics Summary of Critical Issues and Complexities

NDA 206256 was submitted in accordance with 505(b)(1) of the Federal Food, Drug and Cosmetic Act for the use of belinostat to treat patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). Belinostat is a pan-inhibitor of histone deacetylase (HDAC) Class I, Class II, and Class IV enzymes. It is intended to be administered as a single agent and the recommended dose is 1,000 mg/m^2 administered as an intravenous (IV) infusion over 30 minutes on Days 1-5 of a 21 day cycle; cycles can be repeated until disease progression or unacceptable toxicity.

The pharmacokinetics (PK) and pharmacodynamics of belinostat have been evaluated in 8 clinical studies. The PK/pharmacodynamic studies included:

- 1 monotherapy (IV) study in patients with relapsed or refractory PTCL
- 3 monotherapy (IV) studies in patients with advanced malignancies
- 3 combination therapy (IV) studies in patients with advanced malignancies
- 1 monotherapy (oral) study in patients with advanced malignancies

The proposed commercial product is formulated as a lyophilized powder containing 500 mg/vial of belinostat and (b) (4) L-Arginine (1000 mg/vial). As indicated in the proposed labeling, the product is reconstituted in 9 mL Sterile Water for Injection. Prior to administration, the reconstituted belinostat (50 mg/mL) is admixed with 0.9% saline to the desired strength for infusion. However, the clinical formulation was previously manufactured as a (b) (4) formulation, which consisted of belinostat (b) (4) and L-arginine (b) (4) and required refrigerated storage. The (b) (4) product maintains the same components and composition as the (b) (4) formulation, and it was agreed to by FDA that bioequivalence studies were not needed to support these major manufacturing changes (see *EOP2 CMC Meeting held on 10 December 2009 – Drs. John Duan and Patrick Marroum for Biopharmaceutics*).

Further, because belinostat for Injection is administered as an IV solution, no other data on biopharmaceutics classification system (BCS) assignment, bioavailability, bioequivalence, or food effects are presented in this submission. Thus, in accordance with the division of review responsibilities between Clinical Pharmacology and Biopharmaceutics under the 13 September 2013 memorandum of understanding, Clinical Pharmacology will evaluate all other PK and clinical pharmacology data submitted in this NDA. No further action is warranted from Biopharmaceutics.

CMC FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
*	**If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.**			
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			N.A.

	Parameter	Yes	No	Comment
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
8.	Are `drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		

	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment or claim of categorical exclusion been provided?	X		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		
24.	Does the section contain controls of the final drug product?	X		
25.	Has stability data and analysis been provided to support the requested expiration date?	X		
26.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
27.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
28.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
29.	If appropriate, is a separate microbiological section included assuring sterility of the drug product	X		

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
30.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
026926	II	Spectrum Pharmaceuticals, Inc. 157 Technology Drive Irvine, CA 92618	Belinostat DS	04-Dec-2013	--
(b) (4)	III	(b) (4)		12-Feb-2013	--
	II			07-Fed-2013	
	III			07-Feb-2013	--

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
31.	Has the draft package insert been provided?	X		
32.	Have the immediate container and carton labels been provided?	X		

BIOPHARMACEUTICS FILING REVIEW CHECKLIST

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS **A. INITIAL** OVERVIEW OF THE NDA APPLICATION FOR FILING				
	PARAMETER	**YES**	**NO**	**COMMENT**
33.	Does the application contain dissolution data?		x	
34.	Is the dissolution test part of the DP specifications?		x	
35.	Does the application contain the dissolution method development report?		x	
36.	Is there a validation package for the analytical method and dissolution methodology?		x	
37.	Does the application include a biowaiver request?		x	
38.	Does the application include a IVIVC model?		x	
39.	Is information such as BCS classification mentioned, and supportive data provided?		x	
40.	Is information on mixing the product with foods or liquids included?		x	
41.	Is there any in *vivo* BA or BE information in the submission?	x		
42.	Is there a modified-release claim? If yes, address the following: a.) Is there information submitted to support the claim in accordance with 320.25(f)? b.) Is there information on the potential for alcohol-induced dose dumping? c.) Is there a site comparability protocol?		x	

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
43.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		
44.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			
45.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		x	

This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

See appended electronic signature page}
Janice Brown M.S.
CMC Lead
Division 1
Office of New Drug Quality Assessment

{See appended electronic signature page}
Minerva Hughes, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

{See appended electronic signature page}
Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

{See appended electronic signature page}
Ali Al-Hakim, Ph.D.
Branch Chief
Division 1
Office of New Drug Quality Assessment

Initial Quality Assessment

SUMMARY

Belinostat is an inhibitor of histone deacetylases (HDAC) Class I and II enzymes. Histones are the major proteins in chromatin, assisting in the packaging and assembly of deoxyribonucleic acid (DNA) into nucleosomes, and play an important regulatory role in gene expression. In general, acetylation of lysine residues (ε-amino groups) on nucleosomal histones is associated with transcriptional activation, while deacetylation is associated with condensation of chromatin and transcriptional repression. Belinostat induces an increase in acetylation of both histone and non-histone proteins, thereby influencing chromatin accessibility and, ultimately, gene transcription. The hydroxamate region of belinostat chelates a zinc ion, which is necessary for activity of the HDAC family of enzymes. It is specific for the zinc-containing HDAC family and does not inhibit other zinc-containing enzymes.

Beleodaq (belinostat for injection) is supplied as a sterile lyophilized yellow solid containing belinostat and L-Arginine, USP. The drug product is supplied in single-use 30 mL clear glass vials with coated stoppers and aluminum crimp seals with "flip-off" caps. Each vial contains 500 mg belinostat and 1000 mg L-Arginine, USP. Beleodaq is intended for intravenous administration after reconstitution with 9 mL Sterile Water for Injection, and the reconstituted solution is further diluted with 250 mL 0.9% Sodium Chloride Injection prior to infusion. Beleodaq must be stored at 25°C (77°F) in its outer carton until use.

The recommended dosage regimen of Beleodaq for patients is 1000 mg/m² administered IV over 30- minute period on Days 1-5 of a 21-day cycle. The individual dose was determined using the body surface area (BSA) based on actual body weight of the patient.

DRUG SUBSTANCE

1.0 The applicant provided a letter of authorization allowing the agency to review the confidential information in DMF No. 26926. This DMF has not been previously reviewed.

2.0 There was an agreement on the starting material designation of (b) (4) in a EOP2 meeting held on 10-Dec-2009.

3.0 (b) (4). Belinostat is slightly soluble in distilled water, polyethylene glycol 400, (b) (4) and freely soluble in ethanol. (b) (4) . Based on the *in vitro* and *in vivo* assays, belinostat is genotoxic.

4.0 There have been two different manufacturing processes used through the clinical development of belinostat: Process Ia and Process IIa. Process Ia was the original

manufacturing method by which belinostat was produced during the preclinical development at a scale of up to (b) (4) This process was further refined by (b) (4) to be capable of producing belinostat (b) (4) (Process Ib). Process IIa was used to produce the 3 registration batches at (b) (4) Table 1 provides a summary of the manufacture, scale, process, time period, and usage of the drug substance.

Table 1: Manufacturer of Belinostat Drug Substance

Manufacturer	(b) (4)		
Scale of manufacture			
Process	Ia	Ib	IIa (proposed commercial process)
Period of manufacture	May 2001 – June 2005	June 2005 – March 2007	March 2007 - present
Development batches / Manufacturing year	PR1-40/2001 PR1(1)-67/2001 PR1(2)-12C/2001 PR1(2)-18A/2001 PRX(1)-21B/2002 PRQ1(3)-10/2003	NA	6AK0327/2006 11AK0033A/2011
Clinical batches / Manufacturing year	PRX1(4)-19/2003 PRX1(5)-19/2003 PRX1(6)-19/2004 PRX1(6)-40/2004 PRX1(6)-54/2004 PRX1(7)-17/2005 PRX1(7)-35/2005 PRX1(8)-8/1/2005	GF802/2005 HA804/2006 IB805/2007	02070044/2007[a] 02070035/2007[b] 02070037/2007[b] 02090146/2009[b] 02110036/2011
Usage of drug substance	Safety, Preclinical Drug Product Process Development Clinical Stability	Safety, Preclinical Drug Product Process Development Clinical Stability	Drug Product Process Development Clinical Stability

[a] (b) (4)

[b] Drug Substance Registration Batches

Abbreviations: (b) (4)., NA=not applicable (b) (4)

5.0 The (b) (4) manufacturing flow diagram of the synthesis of belinostat drug substance is reproduced in figure 1.

Figure 3.2.S.2.2-1 Belinostat Drug Substance Synthetic Scheme

(b) (4)

6.0 A complete list of drug substance manufacturing facilities is appended in attachment 1.

7.0 Impurities

7.1 Organic Impurities - Summarized in table 2 are the observed organic impurities levels, qualified level in toxicology studies, and drug substance specification. Organic impurities are either below the qualification threshold or identification threshold.

(b) (4)

Table 2: Organic Impurities

Organic Impurity Structure Source	Origin	Drug Substance Specification	Comment
(b) (4)			

Organic Impurity Structure Source	Origin	Drug Substance Specification	Comment
[redacted]			

7.2 Inorganic Impurities – Potential inorganic impurities [redacted] are tested by Residue on Ignition/Sulfated Ash harmonized method with a limit of NMT [redacted]% in the final release of belinostat drug substance.

7.3 Heavy Metals/ [redacted] - Heavy Metals testing is performed by the USP Heavy Metals Method II with a limit of NMT [redacted] and for [redacted] the testing is performed by atomic absorption spectroscopy with a limit of NMT [redacted]

8.0 The belinostat drug substance specification is appended as attachment 3.

9.0 Belinostat is packaged in [redacted] to ensure the integrity of the packaging during shipment. [redacted]

10.0 Stability

10.1 The applicant submitted long-term, intermediate and accelerated stability data for 3 batches of drug substance (see table 3). Note that there was a change in the primary container; [redacted]. A 6-month accelerated stability study at 40°C/75% RH was performed and the results showed no differences in the stability of the drug substance between the two [redacted] The applicant has commitment to place all validation batches ([redacted] on stability according to the proposed stability protocol.

Table 3 – Primary Drug Substance Stability Batches

Batch No.	Manufacture		Batch Size (Kg)	Study No.	Study Design	Data presented in the Application
	Site	Date				
02070035	(b) (4)	Mar 2007	(b) (4)	S07-017	60 months 25°C/60%RH 60 months 30°C/65%RH 6 months 40°C/75%RH	60 months 25°C/60%RH 60 months 30°C/65%RH 6 months 40°C/75%RH
02070037		Apr 2007		S07-017	60 months 25°C/60%RH 60 months 30°C/65%RH 6 months 40°C/75%RH	60 months 25°C/60%RH 60 months 30°C/65%RH 6 months 40°C/75%RH
02090146		Sep 2009		S09-045	60 months 25°C/60%RH 60 months 30°C/65%RH 6 months 40°C/75%RH	36 months 25°C/60%RH 36 months 30°C/65%RH 6 months 40°C/75%RH
02070035		Mar 2007		S11-048	6 months 40°C/75%RH	6 months 40°C/75%RH

10.2 Quality attributes monitored during stability testing were within the proposed limits at all storage conditions.

10.3 The applicant has proposed a retest period of (b) (4) when stored at the recommended storage condition (b) (4)

10.4 Photostability data show one new related impurity at (b) (4) was observed. This impurity has not been observed in any of the primary stability studies. Based on this data, belinostat is considered (b) (4)

DRUG PRODUCT

11.0 Beleodaq is supplied as a sterile lyophilized yellow solid containing belinostat and L-Arginine, USP. The drug product is supplied in single-use 30 mL clear glass vials with coated stoppers and aluminum crimp seals with "flip-off" caps. Each vial contains 500 mg belinostat and 1000 mg L-Arginine, USP. Beleodaq is intended for intravenous administration after reconstitution with 9 mL Sterile Water for Injection, and the reconstituted solution is further diluted with 250 mL 0.9% Sodium Chloride Injection prior to infusion.

12.0 Belinostat for injection is manufactured and tested by (b) (4) The companies listed in attachment 2 are involved in the manufacture, testing, labeling, packaging, and distribution of the drug product.

13.0 The composition of the Belinostat for injection is reproduced in the table 4.

Table 4: Composition of Belinostat for Injection, 500 mg/vial

Component	Function	Quantity (mg/vial)	Quality Standard
Belinostat	Active	500	In-house
L-Arginine (a)	(b) (4)	1000	Ph.Eur/USP
(b) (4)		(b) (4)	Ph.Eur/USP
			NF/Ph.Eur

(a) (b) (4)
(b) (b) (4)

14.0 The drug product manufacturing flow diagram and drug product specification are reproduced in attachments 4 and 5, respectively. The drug product manufacturing was optimized during development; the (b) (4) formulation was converted to a lyophilized powder. The reconstituted product is identical in composition to the (b) (4) formulation. In an EOP2 CMC meeting minutes dated 11-Jan-2010, bioequivalence studies were not required to qualify this change from the (b) (4) to the 500 mg/vial lyophilized powder.

15.0 DEGRADANTS - The main degradants are the result of (b) (4) . Belinostat related degradants are described in Table 5.

Table 5: Belinostat Related Impurities

Impurity	Relative Retention Time	Identification Criteria	Description
(b) (4)			

Impurity	Relative Retention Time	Identification Criteria	Description
(b) (4)			

16.0 The primary container closure system consists of Type I tubing (b) (4) glass vials with a 20 mm neck size, a 20 mm diameter lyophilizer stopper and an aluminum flip-off seal. LOAs were provided for vials (DMF (b) (4)) and stoppers (DMF (b) (4) and (b) (4)

17.0 DRUG PRODUCT STABILITY STUDIES

17.1 The applicant submitted 12 months of long term and 6 months of accelerated stability data generated on three (3) registration batches manufactured at (b) (4) the proposed commercial manufacturing site. Stability data generated on four (4) batches manufactured at (b) (4) are included as the supportive data for Belinostat for Injection (500 mg/vial). A summary of the batches used to support the shelf life is shown in table 6.

Table 6: Stability Studies Conducted on Registration Batches

Drug Product Batch No.	Drug Substance Batch No.	Manufacture		Batch Size Site Date (vials)	Batch Use	Amount of Stability Data		
		Site	Date			25°C/60% RH	30°C/65% RH	40°C/75 % RH
11J27	02110036	(b) (4)	Oct 2011	9,000	Clinic Stability	12 months	12 months	6 months
12A17	02110036	(b) (4)	Jan 2012	4,500	Clinic Stability	12 months	12 months	6 months
12B01	02110036	(b) (4)	Feb 2012	4,500	Clinic Stability	12 months	12 months	6 months
1803795	02070037	(b) (4)	Oct 2009	10,000	Clinic Stability	36 months	36 months	6 months
1859721	02090146	(b) (4)	Apr 2010	10,000	Clinic Stability	24 months	24 months	6 months
1936443	02070037 02090146	(b) (4)	Apr 2010	10,000	Clinic Stability	24 months	24 months	6 months
2060256	02090146	(b) (4)	Oct 2010	10,000	Clinic Stability	24 months	24 months	6 months

17.2 All test stability data meets the proposed specification. No significant changes were seen in the stability-indicating parameters, such as assay and impurities, pH, or reconstitution time, for any of the registration or supportive batches for both the long-term and accelerated storage conditions.

17.3 The applicant is requesting a 24 month shelf life for Belinostat for Injection (500 mg/vial) when stored at 20 – 25°C.

17.4 Photo Stability - No difference in the tested parameters was observed between any of the light exposed samples and the dark controls. Based on the results of the study, Belinostat for Injection is photo stable and reconstituted and admixed Belinostat for Injection is photo stable at 25°C when subjected to ambient building lighting (fluorescent) for up to 48 hours.

17.5 In-Use Compatibility Study

The physicochemical stability was assessed over a 24 hour period and included evaluation of appearance, assay, impurities, pH and particulates. Vials of Belinostat for Injection were reconstituted with 9 mL Sterile Water for Injection. The vials were then stored at 25°C/60% RH, and sampled and tested at 0, 4, 8, and 24 hours. The reconstituted vials were found to be stable with respect to appearance, assay, impurities, pH, and particulate matter over the duration of the study (24 hours).

In-use studies have demonstrated chemical and microbiological stability of the reconstituted solution and admixtures of belinostat drug product for up to 24 hours and 72 hours, respectively, when stored at 25°C. In some of the admixture stability studies, particulate matter was observed in the IV infusion bags. As a result, the admixed drug product must be filtered through a 0.22 μm in-line filter prior to administration.

18.0 Environmental Assessment: The applicant has submitted a claim for categorical exclusion under 25.31(b) which states that use of this product will not cause the concentration of the drug substance active moiety to be one part per billion (1 ppb) or greater at the point of entry into the aquatic environment.

Attachment 1: Belinostat Drug Substance Manufacturing Sites

Name and Address	Responsibilities
(b) (4)	Drug substance manufacturing and quality control testing (except for microbial and bacterial endotoxin testing), as well as packaging and storage
	Drug substance stability storage and testing
	Bacterial endotoxin testing
	Microbial testing

Attachment 2: Drug Product Manufacturing Sites

Name and Address	Responsibilities
(b) (4)	Drug Product manufacturing, in-process and release testing, stability storage and stability testing, labeling and packaging
	Stability storage and stability testing
	Alternate site for Drug Product labeling and packaging

Attachment 3: Belinostat Drug Substance Specification

Table 3.2.S.4-1 Specification

Test	Method	Limits
(b) (4)		

Attachment 4: Belinostat for Injection Drug Product Manufacturing Flow Diagram

Figure 1 Process Flow Diagram

Processing Step	Processing Parameters / In-Process Controls
[redacted]	(b) (4)

Attachment 5: Belinostat for Injection Specification

Table 9 Drug Product Specification

Test	Method (Procedure No.)	Limits
		(b) (4)

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