CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205266Orig1s000

CHEMISTRY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

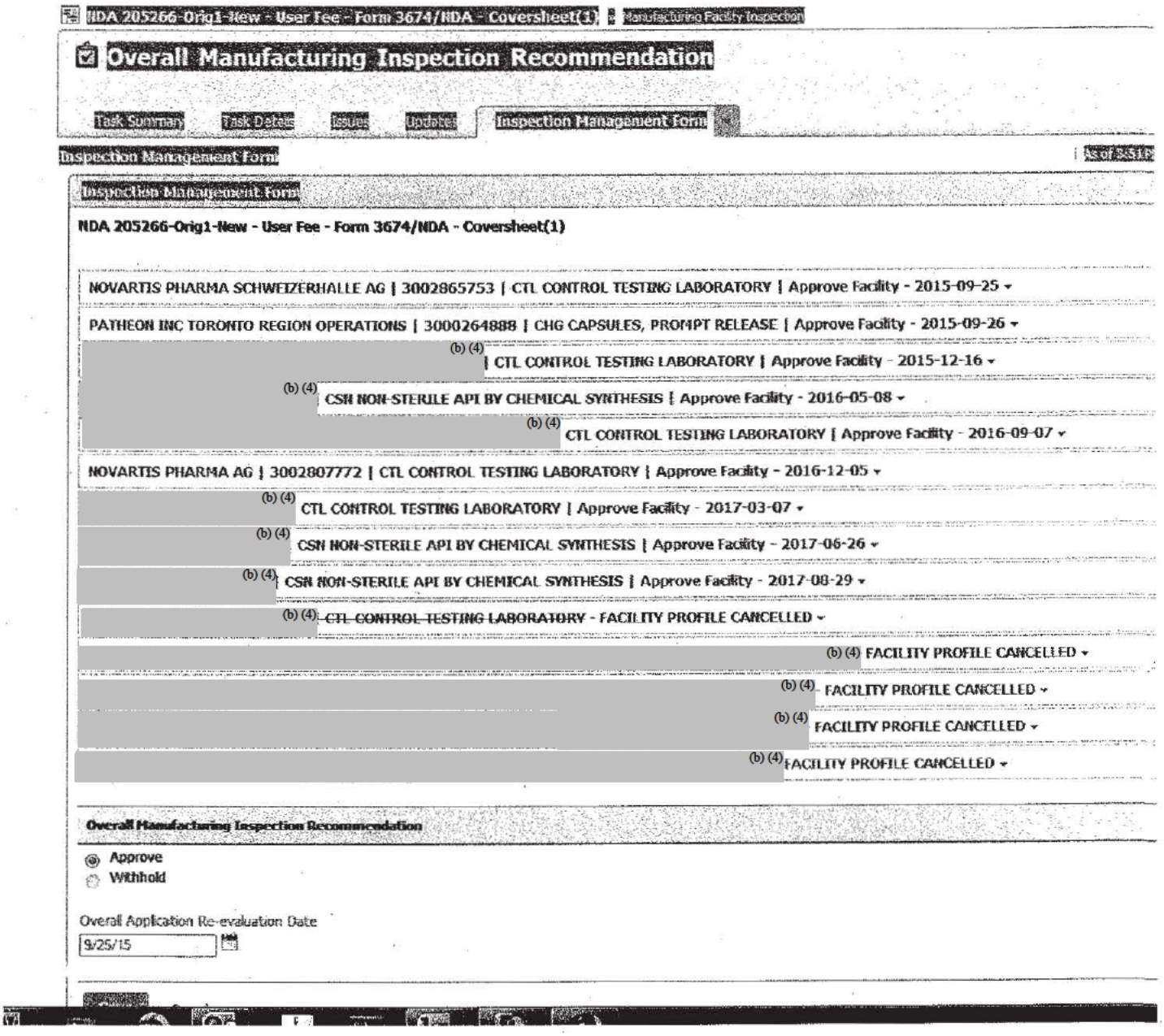
Memorandum

Date: June 1, 2015

From: Anuja Patel, M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266: Facility Inspection

Facility Inspection review can be found on page 125 of the Quality Assessment Review.



QUALITY ASSESSMENT

<< applicable option would be selected from a drop down list>>
First Approval for Indication/First Generic
Expedited or Breakthrough Review

Recommendation:
NDA: Approval /Complete Response

NDA 205266
Review #1
Review Date

Drug Name/Dosage Form	Sonidegib Capsules
Strength	200 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Novartis Pharmaceutical Corp.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE
S-000 new NDA	09/26/14
S-001 (b) (4) MDD	10/08/14
S-002 S2, S4, P2, P8	10/23/14
S-010 labeling	11/20/14
S-011 QC response	01/06/15
S-014 labeling	01/23/15
S-019 API	02/06/15
S-025 API	03/17/15
S-028 Micro, biopharm, API, P2, P3	03/24/15
S-031 biopharm	03/30/15
S-034 P3	04/07/15
S-035 P81, P82	04/15/15
S-036 P51 dissolution	04/14/15
S-039 P33	04/17/15
S-040 P51 corrected dissolution	04/16/15
(b) (4)	
S-046 P2, P51, P52, P82	04/30/15
S-047 labels, labeling	05/06/15

Quality Review Team

CHEMISTRY REVIEW

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Ben Stevens/Donna Christner	Branch 2/New Drug API
Drug Product	William Adams/Olen Stephens	Branch 2/New Drug DP
Process	Yubing Tang/ Chatterjee, Sharmista	Branch 1 / Office of Process and Facilities
Microbiology	Stephen Langille/ Bryan Riley	Branch 3 / Office of Process and Facilities Microbiology
Facility	Robert Wittorf/ Mahesh Ramanadham	Branch 2 / Office of Process and Facilities
Biopharmaceutics	Okpo Eradiri/Angelica Dorantes	Branch 1/ New Drug Product Biopharmaceutics
Project/Business Process Manager	Teicher Agosto	Branch 4/ Office of Program and Regulatory Operations
Application Technical Lead	Liang Zhou	Branch 2/ New Drug
Laboratory (OTR)	N/A	
ORA Lead	Sharon Thoma	ORA
Environmental Assessment (EA)	William Adams	Branch 2/New Drug DP

Table of Contents

Table of Contents **3**

Quality Review Data Sheet **4**

Executive Summary **6**

Primary Quality Review **11**

ASSESSMENT OF THE DRUG SUBSTANCE 11

2.3.S DRUG SUBSTANCE 11

ASSESSMENT OF THE DRUG PRODUCT 55

2.3.P DRUG PRODUCT 55
R.2 Comparability Protocols 101

ASSESSMENT OF THE PROCESS 102

2.3.P DRUG PRODUCT 102
R.2 Comparability Protocols 123
R.2 Comparability Protocols 124

ASSESSMENT OF THE FACILITIES 125

2.3.S DRUG SUBSTANCE 125
2.3.P DRUG PRODUCT 127

ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION 129

ASSESSMENT OF MICROBIOLOGY 139

2.3.P.6 Reference Standards or Materials 140

A APPENDICES 140

A.2 Adventitious Agents Safety Evaluation 140

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1 141

Labeling & Package Insert 141

II. List of Deficiencies To Be Communicated 150

III. Attachments 151

IV. Administrative 152

Quality Review Data Sheet

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

2. **RELATED/SUPPORTING DOCUMENTS:**

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
	Type II					
(b) (4)	Type III		(b) (4)	Adequate		Based on information in NDA
	Type III			Adequate		Based on information in NDA
	Type III			Adequate		Based on information in the NDA
	Type III			Adequate		Based on information in the NDA
	Type III			Adequate		Based on information in the NDA
	Type III			Adequate		Based on information in NDA
	Type III			Adequate		Based on information in NDA
	Type IV *(if applicable)*					
	Other					

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	102961	active
IND	(b) (4)	
IND		
IND		

3. **CONSULTS:**

QUALITY ASSESSMENT
NDA # 205266

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics		N/A		
Pharmacology/Toxicology	Complete	Adequate	04/16/15	Alex Putman
CDRH		N/A		
Clinical		N/A		
Statistics	Complete	Adequate with comments	01/09/15	Zhuang Miao

Executive Summary

I. Recommendations Approval is recommended

A. Recommendation and Conclusion on Approvability

This application is recommended for approval from a CMC perspective; an overall "approval" recommendation from has been received from the facilities reviewer. Capsules are packaged in two configurations - a 30-count HDPE bottle with 1 gram desiccant and a 30-count blister pack – which are to be stored at 25C with excursions to 15-30C (b) (4)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable None

II. Summary of Quality Assessments

A. Drug Substance [USAN Name] Quality Summary

Sonidegib phosphate is *N*-{6-[(2*R*, 6S)-2, 6-dimethylmorpholin-4-yl] pyridin-3-yl}-2-methyl-4′-(trifluoromethoxy)-[1, 1′ -biphenyl]-3-carboxamide diphosphate ($C_{26}H_{26}F_3N_3O_3 \cdot 2H_3O_4P$, MW = 681.50). As per the salt nomenclature policy, it is designated as sonidegib throughout the labeling. Sonidegib phosphate can exist in two common polymorphic forms: (b) (4)
(b) (4)

The sonidegib phosphate drug substance is manufactured using a (b) (4)
(b) (4)

The final drug substance (b) (4)
(b) (4)

(b) (4)

The sonidegib phosphate drug substance release specifications include: appearance, particle size (laser light diffraction), (b) (4) identity (IR and XRPD), related substances (HPLC and GC), solvents (GC), heavy metals (b) (4) (b) (4) microbial enumeration tests, total aerobic microbial count (TAMC), total combined yeasts/molds (TYMC), specified microorganisms (*E. coli*), and assay (HPLC and titration). (b) (4) Acceptance criteria for related substances are set based on ICH Q3A with the exception of (b) (4) The proposed limits for these impurities were found to be adequate based on consultation with Pharm. Tox.

The sonidegib phosphate drug substance is packaged in (b) (4) (b) (4) (b) (4) The sponsor states that (b) (4) packaging components meet regulations (b) (4).

The applicant has proposed a retest period of (b) (4) months for the sonidegib phosphate drug substance when stored below (b) (4) °C, based on the results of 18-month long-term stability at 25 °C/60% RH and 6-month accelerated stability at 40 °C/75% RH from three primary stability batches of this drug substance, as well as additional supporting long-term and accelerated stability results using related packaging materials. No significant changes in the drug substance strength and purity were noted. A statistical analysis was provided to support extrapolation of the 18 month test results to a (b) (4) month retest. The data was found to support this retest period per ICH Q1E following consultation with Statistics. **The proposed retest period is granted.**

B. Drug Product [sonidegib phosphate] Quality Summary

Sonidegib is a hedgehog pathway inhibitor indicated for the treatment of adult patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy; (b) (4) The recommended dose is one 200 mg HG capsule taken orally once daily (b) (4) The maximum daily dose is 200 mg.

The commercial presentation is an 200 mg strength, immediate release, pink (b) (4) (b) (4) opaque number 00 hard gelatin capsule marked with black (b) (4) imprint "NVR" on the cap and "SONIDEGIB 200MG" on the body. Capsules are packaged in two configurations - a 30-count HDPE bottle with 1 gram desiccant and a 30-count blister pack – which are to be stored at 25°C with excursions to 15-30°C (b) (4) (b) (4).

Product development addressed the need for [redacted]

The formulation uses USP/EP grade excipients and a commercially available capsule composed of gelatin [redacted] The acceptance specifications for ingredients are adequate and appropriately justified.

The sites for manufacture and control have been found to meet cGMP requirements. The manufacturing process and process parameters are well described and appropriately justified.

Process review has found the information in original submission and in the amendments dated 01/09/2015, 03/24/2015/ 04/07/2015, 04/17/2015, 04/22/2015 and 04/30/2015 to be adequate for the proposed manufacturing process.
The manufacturing process for the drug product Sonidegib 200 mg Hard Gelatin Capsule involves the following process steps: [redacted] are identified as critical process steps. The critical process parameters and the operating ranges for each step are appropriately proposed. In-process controls include LOD at [redacted]. Selection of process operating parameter settings and in-process controls are supported by data from pilot scale batch and registration batches, and other relevant formulation and process development information. [redacted] It should be noted during manufacturing [redacted]. Available batch data showed that [redacted] during manufacturing is consistently within the spec. limits of NMT [redacted]%, hence further controls on [redacted] during manufacturing was not warranted.

The proposed specifications for release and stability are acceptable. The proposed tests address appearance, identity, assay, purity, [redacted] drug release and USP requirements. The proposed analytical methods are described in sufficient detail and appropriately validated for their intended purpose. The method for organic impurities has adequate sensitivity. The proposed criteria are justified by USP/EP expectations; primary and supportive batch analysis data; and stability data. The drug release criterion has been accepted by the Biopharm Reviewer and the applicant. Reference standards for drug substance and known organic impurities are described and well characterized.

The proposed packaging systems are appropriately qualified. Components are well described and appropriate acceptance specifications are proposed. Reference to type III DMFs are provided through letters of authorization.

Registration and supportive stability studies are appropriate to address the proposed commercial presentations, and drug substance and drug product manufacturing sites. The study data is adequate to support the proposed label statement and the initial shelf life for each presentation. The protocol and commitments for post approval studies are adequate to support the label storage statement and extension of the initial shelf life.

Draft blister package container and carton labels; bottle labels; and package insert have been submitted. Bottle carton labels are not submitted. Label and labeling text is being negotiated.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	ODOMZO®
Non Proprietary Name of the Drug Product	sonidegib
Non Proprietary Name of the Drug Substance	sonidegib phosphate.
Proposed Indication(s) including Intended Patient Population	for the treatment of patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy
Duration of Treatment	
Maximum Daily Dose	The recommended dose is 200 mg orally once daily (2)
Alternative Methods of Administration	None

D. Biopharmaceutics Considerations

1. BCS Designation:
   - Drug Substance: (b) (4) [redacted]
   - Drug Product: N/A

2. Biowaivers/Biostudies
   - Biowaiver Requests: N/A
   - PK studies: Not reviewable from Biopharmaceutics perspective.
   - IVIVC: N/A

E. Novel Approaches N/A

F. Any Special Product Quality Labeling Recommendations None

G. Process/Facility Quality Summary (see Attachment A)

H. Life Cycle Knowledge Information (see Attachment B)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

Liang Zhou -S

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Primary Quality Review

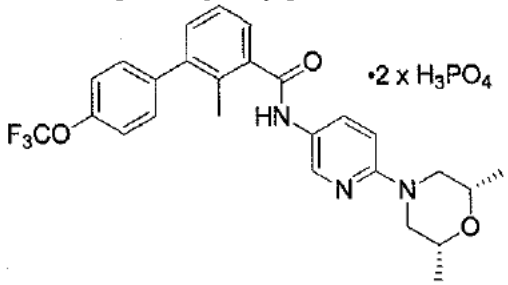
ASSESSMENT OF THE DRUG SUBSTANCE

2.3.S DRUG SUBSTANCE

2.3.S.1 General Information

Applicant's Response:

- USAN Name: **Sonidegib phosphate** (**sonidegib** for free base, previously known as erismodegib)
- Chemical Name: (1) [1,1′-Biphenyl]-3-carboxamide, *N*-[6-[(2*R*,6*S*)-2,6-dimethyl-4-morpholinyl]-3-pyridinyl]-2-methyl-4′-(trifluoromethoxy)-, rel-, phosphate (1:2); (2) *N*-{6-[(2*R*,6*S*)-2,6-Dimethylmorpholin-4-yl]pyridin-3-yl}-2-methyl-4′-(trifluoromethoxy)-[1,1′-biphenyl]-3-carboxamide diphosphate.



- Structure:
- Molecular Formula: $C_{26}H_{26}F_3N_3O_3 \cdot 2H_2PO_4$
- CAS: 1218778-77-8
- MW: 681.49
- Pharmacological Class: Hedgehog pathway inhibitor
- Physical State: White to slightly yellow powder
- pKa: 4.3 (free base)
- Chirality: Achiral
- Polymorphism: (b) (4)

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Reviewer's Assessment:

- The provided acceptance criteria for the DS [redacted] (b) (4) [redacted] (b) (4) Several tests are not included [redacted] (b) (4) [redacted] and these are justified.
- The proposed stability testing protocol extends the present studies out to [redacted] (b) (4) months and is adequate.
- The post-marketing stability commitment statement provided by the sponsor currently lacks [redacted] (b) (4). The following IR was sent (04-MAR-2015):
  Reviewer Question: *Update the stability commitment for sonidegib (section 3.2.S.7.2)* [redacted] (b) (4) [redacted]
  Response Summary: The sponsor updated the stability commitment as requested.
  Response Assessment: Adequate.

Overall Assessment: ADEQUATE

OVERALL ASSESSMENT AND SIGNATURES: DRUG SUBSTANCE

Reviewer's Assessment and Signature:

ADEQUATE Benjamin Stevens -S

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Date: 2015.05.15 11:20:35 -04'00'

Supervisor Comments and Concurrence:

Donna F. Christner -S

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Note: additional reviewers can be added, as appropriate

ASSESSMENT OF THE DRUG PRODUCT

2.3.P DRUG PRODUCT

The recommended dose is stated to be 200mg once daily [redacted] (b) (4) [redacted]. Maximum daily dose is stated to be [redacted] (b) (4) 200mg [redacted] (b) (4)

2.3.P.1 Description and Composition of the Drug Product

Sonidegib is a hedgehog pathway inhibitor indicated for the treatment of adult patients with locally advanced basal cell carcinoma (BCC) who are not amenable to

curative surgery or radiation therapy; (b) (4). The recommended dose is one 200mg HG capsule taken orally once daily (b) (4)

16. Are there any scientific or regulatory concerns about the proposed composition of the drug product?

The commercial presentation is an immediate release, pink (b) (4) opaque (b) (4) HG capsule with black (b) (4) imprint "NVR" on cap and "SONIDEGIB 200MG" on body packaged into 30-count HDPE bottles with 1 gram desiccant and 30-count blister packs to be stored at USP CRT (b) (4) (b) (4)

Drug Product Composition

Ingredient	***function***	***mg/capsule***
Sonidegib, in-house[1]	active	200.00
Crospovidone, EP/NF	(b) (4)	(b) (4)
Lactose monohydrate, EP/NF		
Poloxamer (b) (4) EP/NF		
Sodium Lauryl Sulfate, EP/NF		
Magnesium Stearate, EP/NF[2]		
Colloidal Silicon Dioxide, EP/NF		
(b) (4)		
fill weight		
Pre-printed Capsule Shell		
total capsule weight		534.60
(b) (4)		

Capsule Shell Composition

Ingredient	***Function***	***mg/capsule***
Gelatin, EP/NF[1]	(b) (4)	(b) (4)
(b) (4)		
Titanium Dioxide (b) (4)		
Iron Oxide, red (b) (4)[2]		
Printing Ink, black		
(b) (4)		

Imprinting Ink Composition

Ingredient	***Grade***
Shellac	EP/NF
Iron Oxide (b) (4)	EU/231/2012, 21 CFR
Ammonium Hydroxide	EP/NF

Reviewer's Assessment:

The market product is a single strength and dosage form in 2 packaging presentations. Acceptable in that the CMC information is complete.

2.3.P.2 Pharmaceutical Development 33333

17. Does the information described in the pharmaceutical development section support the proposed product design, commercial formulation, dosage form, compatibility, specification, and overall control strategy of the drug product?

Amendment S-000
Novartis Document 6003228_P2_M_840_2 dated 09/13/14, 30 pp: Pharmaceutical Development
DRUG SUBSTANCE

(b) (4)

(b) (4)

DRUG PRODUCT

Formulation Development

(b) (4)

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proposed label storage condition of USP CRT. Applicant has committed to submit the completed studies in the annual reports.

30-Count Bottle: The overall data supports the proposed 18M long term shelflife (b) (4) and the proposed label storage condition of USP CRT. Applicant has committed to submit the completed studies in the annual reports.

(b) (4)

[redacted]

R.2 Comparability Protocols

26. Is a Comparability Protocol included in the application for post approval changes that might affect drug product quality including sterility assurance? If so, what post-approval changes are anticipated? How will the changes be reported and how will the validation studies be designed to support these changes?

Reviewer's Assessment:

None are proposed.

OVERALL ASSESSMENT AND SIGNATURES: DRUG PRODUCT

Reviewer's Assessment and Signature:

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Supervisor Comments and Concurrence:

Olen Stephens -S

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Note: additional reviewers can be added, as appropriate

ASSESSMENT OF THE PROCESS

This review covers the information regarding drug product manufacturing process provided in following submissions:

1.	Original Submission, 09/26/2014 (SDN00)
2.	Amendment 01/09/2015 (SDN11)
3.	Amendment 03/24/2015 (SDN28)
4.	Amendment 04/07/2015 (SDN34)
5	Amendment 04/17/2015 (SDN39)
6.	Amendment 04/22/2015 (SDN41)
7.	Amendment 04/30/2015 (SDN46)

2.3.P DRUG PRODUCT

2.3.P.3 Manufacture

BATCH FORMULA:

27. Does the provided batch formula reflect the proposed composition and that of the registration batches?

Information Provided

- For Commercial Batches (Section P.3.2.)

Table 2-1 Batch formula for Sonidegib 200 mg capsule fill

Ingredient	Reference to standards	Amount per batch (kg)
(b) (4)		(b) (4)
Sonidegib diphosphate[1,2]	Novartis monograph	
Crospovidone	Ph.Eur./ NF	
Lactose monohydrate	Ph.Eur./ NF	
(b) (4) Poloxamer (b) (4)	Ph.Eur./ NF	
(b) (4) Sodium lauryl sulfate	Ph.Eur./ NF	
(b) (4)	Ph.Eur./ USP	
(b) (4)		
Magnesium stearate[4]	Ph.Eur./ NF	
(b) (4) Colloidal silicon dioxide	Ph.Eur./ NF	
Total capsule fill batch weight[5]		

(b) (4)

Table 2-2 Batch formula for Sonidegib 200 mg hard gelatin capsule

Ingredient	Reference to standards	Amount per batch (kg)
Capsule fill (b) (4)	--	(b) (4)
Empty capsule shell, pre-printed (theoretical weight)	Novartis monograph	
Total batch weight		

[1] Refer to Table 2-1.

Reviewer's Assessment (Review #1): Adequate

(b) (4)

(b) (4) The review found that the executed batch record for validation used the proposed batch formula and commercial scale (b) (4). Also, the proposed commercial formulation/composition was used for all the registration batches and validation batches. The release test results for those batches met the specification limits (Section P.5.4). It should be noted that the amount of drug substance accounts for (b) (4)% (w/w) of the capsule fill.

In the below table *Clinical Batches and Registration Batches*, the reason that the batch size for validation batches (b) (4)

(b) (4)

Clinical Batches and Registration Batches (Section P.5.4.)

Batch no #	Manufacturing site	Date of manufacture	Batch size (capsules)	Use of batch	Drug substance batch(es) used	Source of drug substance batch(e
X280 1110	Patheon	Nov 2010	(b) (4)	Clinical[1]	(b) (4)	
X193 0711	Patheon	Jul 2011		Clinical[1]		
X278 0613	Patheon	Aug 2013		Clinical[1]		
X159 0812	Patheon	Sep 2012		Registration stability (b) (4) HDPE bottle and blister)		
X328 0813	Patheon	Aug 2013		Validation		
X331 0813	Patheon	Aug 2013		Registration stability (90 cc (b) (4) HDPE bottles) and Validation		
X332 0813	Patheon	Aug 2013		Registration stability (90 cc (b) (4) HDPE bottles) and Validation		
X461 1213	Patheon	Jan 2014		Validation		
X462 1213	Patheon	Jan 2014		Validation		
X464 1213	Patheon	Jan 2014		Validation		

[1] Used in pivotal clinical trial CLDE225A2201

The information appears to demonstrate that the manufacturer has accumulated adequate knowledge for the proposed process and drug product since (b) (4) batches have been manufactured according to the proposed formula and in the scale equivalent to the proposed commercial scale. The release results for all the batches met the proposed specification (see table summary below).

Registration Batches vs. Commercial Batches (Section P.8.1.1.)

Comparison criteria	Registration batches	Commercial batches	Evaluation
Dose strength	200 mg	200 mg	No change
Composition	(b) (4)		
Capsule shell			
Manufacturing site			
Manufacturing process			
Batch size			
Release specifications			
Drug substance			
Packaging			

DESCRIPTION OF THE MANUFACTURING PROCESS AND PROCESS CONTROLS

28.

- Schematic of the process flow diagram with the in-process controls is copied below.

Information Provided in 3.2.P.3.3

(Note: In original submission dated 09/26/2014, the applicant provided inadequate information with respect to the drug product manufacturing process and process controls. Information Requests were included in Day 74 letter. The applicant responded all the IRs in 01/09/2015 amendment. This review covers the current (updated) information in Global Submission System).

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(b) (4)

[redacted]

- Executed batches in comparison with the proposed commercial batches

Reviewer's Assessment (#1): Adequate

The applicant provided an executed batch record for [redacted] (b) (4) under 3.2.R in original submission. In 01/09/2015 Amendment, the applicant added an executed batch record for [redacted] (b) (4) for a validation batches in response to the Agency's request in 74 Letter. The range settings for the defined CPP are found to be consistent with those in P.3.3.

27. Do the proposed manufacturing process and controls assure sterility/microbial limits of the final drug product?

Reviewer's Assessment:

Not applicable as the proposed drug product is not sterile product. A separate micro review for this NDA was conducted by OPF/DMA.

R.2 Comparability Protocols

28. Is a Comparability Protocol included in the application for manufacturing process or manufacturing site post approval changes? If so, what post-approval changes are specified? What is the method of evaluation of the changes and the acceptance criteria for the change?? How will the changes be reported?

Reviewer's Assessment:

Not applicable.

OVERALL ASSESSMENT AND SIGNATURES: PROCESS

Reviewer's Assessment: **Adequate**
As can be seen in body of review, all risks associated with [redacted] (b) (4) are found to be adequately controlled. Therefore, from perspective of drug product manufacturing process, the application is found to be **adequate**

Supervisor Comments and Concurrence:

Sharmista Chatterjee -S

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28. Do the proposed manufacturing process and controls assure sterility/microbial limits of the final drug product?

Please see the section titled "Assessment of Microbiology".

Reviewer's Assessment: The drug product is not sterile but the microbial limits specifications and microbiological controls are satisfactory. See the section of this review titled "Assessment of Microbiology" for additional information.

R.2 Comparability Protocols

29. Is a Comparability Protocol included in the application for manufacturing process or manufacturing site post approval changes? If so, what post-approval changes are specified? What is the method of evaluation of the changes and the acceptance criteria for the change?? How will the changes be reported?

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment:

OVERALL ASSESSMENT AND SIGNATURES: PROCESS

Reviewer's Assessment and Signature:

Yubing Tang -S Digitally signed by Yubing Tang -S
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Supervisor Comments and Concurrence:

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Note: additional reviewers can be added, as appropriate

ASSESSMENT OF THE FACILITIES

2.3.S DRUG SUBSTANCE

2.3.S.2 Manufacture

Manufacturer(s)

30. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Points to consider

- Who manufactures the drug substance? List each participant and facility involved in drug substance manufacturing/testing activities and clearly state their function. List the date of the last FDA inspection for each facility involved and the result of the inspection. Identify any historical inspectional findings that could impact the manufacturing of this product?
- For each of the facilities listed above, identify any potential GMP-related issues (e.g., expected in-process testing not being performed, questionable development, unexplained stability failures, data integrity issues, etc)?
- For each of the facilities listed above, are there any indicators that warrant a pre-approval inspection? Explain why or why not.

- For each of the facilities in which a pre-approval inspection was performed, list the date performed, summary of the inspection and any un-resolved observations. Indicate how the potential issues identified above, were/were not mitigated.

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment	Recommendation
(b) (4)		CSM	Manufacturing (b) (4) Stability testing of (b) (4)	9	6	[redacted]	[redacted]	Assigned Inspection
		CSN	(b) (4)	8	6	[redacted]	[redacted]	Acceptable Based on Profile
		CSN	(b) (4)	5	6	0	11	Acceptable Based on Profile
Novartis Pharma AG	3002807772	CTL	DS Testing (b) (4) microbial enumeration test only	9	5	0	14	Acceptable Based on Profile
(b) (4)		CTL	DS Release Testing	9	5	0	14	Acceptable Based on Profile

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment:

Pre-Inspection Evaluation:

The drug substance manufacturing process involves (b) (4) at two different facilities, (b) (4). The process involves several steps, and the review of the application and discussion with the drug substance reviewer revealed no complex or atypical manufacturing. Drug substance manufacturing facilities have familiarity with this manufacturing and testing of the respective drug substance and intermediate unit operations at their respective facilities. (b) (4) (b) (4) Although (b) (4) appear to be high risk, it is due to the current model which includes a New Molecular Entity (NME) as high risk. That being considered, facilities compliance history and familiarity with these types of processes were also taken into consideration for inspectional focus.

No atypical testing is performed at any of the laboratories and all firms have an acceptable inspectional history.

Inspectional results:

The (b) (4) facility was inspected in (b) (4) in which a five item 483 was provided. Although a pre-approval inspection was not performed, the firm made appropriate corrective actions to compliance observations and the classification was considered VAI. An approval with respect to this application was made in Panorama.

All other facilities were approved based on profile and are acceptable for this application.

2.3.P DRUG PRODUCT

2.3.P.3 Manufacture

Manufacturer(s)

31. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Points to consider

- Who manufactures the drug product? List each participant and facility involved in drug substance manufacturing/testing activities and clearly state their function. List the date of the last FDA inspection for each facility involved and the result of the inspection. Identify any historical inspectional findings that could impact the manufacturing of this product?
- For each of the facilities listed above, identify any potential GMP-related issues (e.g., expected in-process testing not being performed, questionable development, unexplained stability failures, data integrity issues, etc)?
- For each of the facilities listed above, are there any indicators that warrant a pre-approval inspection? Explain why or why not.
- For each of the facilities in which a pre-approval inspection was performed, list the date performed, summary of the inspection and any un-resolved observations. Indicate how any of the potential issues identified were/were not mitigated.

Patheon	3000264888	CHG	DP Manufacturing, Release and Stability Testing	[redacted]	14	[redacted]	[redacted]	Assigned Inspection
(b) (4)		CTL	DP release and stability testing	5	5	0	10	Acceptable Based on Profile
(b) (4)		CTL	(b) (4)	9	5	0	14	Acceptable Based on Profile

Reviewer's Assessment:

Pre-inspection evaluation:

Based on review, the Patheon, Toronto (FEI 3000264888) DP manufacturer was the only facility assigned for inspection. A review of the process should a standard drug manufacturing process with (b) (4) One unique note is that there is a (b) (4) during the DP manufacturing process. (b) (4) Discussion with the process and drug product reviewer revealed that there are no inspectional concerns, and any issue can be addressed through informational requests.

Patheon (Toronto) was inspected during 26-30 January 2014. CHG dosage form was reviewed and the inspection was classified VAI. No additional concerns were noted. (b) (4) (b) (4)

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature: Robert H. Wittorf -A

Supervisor Comments and Concurrence:

Mahesh R. Ramanadham -S

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Note: additional reviewers can be added, as appropriate

ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

The Biopharmaceutics assessment is being focused on the evaluation of the dissolution information supporting the proposed dissolution method and acceptance criteria.

32. **Are the in-vitro dissolution method and acceptance criteria adequate for assuring consistent clinical performance of the drug product?**

(b) (4)

The dissolution method and acceptance criteria are therefore adequate for quality control of the proposed drug product. (b) (4)

Summarized below are the dissolution method development, its sensitivity, and acceptance criteria evaluation.

Drug Substance: (b) (4)
(b) (4)

(b) (4)

Drug Product: The proposed drug product for commercialization is a hard gelatin capsule formulation containing 200 mg of sonidegib. The composition of the drug product is shown in Table 31-2.

Table 31-2: Qualitative and quantitative composition of Sonidegib Capsules, 200 mg.

Ingredient	Amount per capsule	Function	Reference to standards
Capsule fill			
Sonidegib diphosphate (corresponding to Sonidegib)	(b) (4) (200.00)	Active ingredient	Novartis monograph
Crospovidone	(b) (4)		Ph.Eur./ NF
Lactose monohydrate			Ph.Eur./ NF
(b) (4) Poloxamer (b) (4)			Ph.Eur./ NF
(b) (4) Sodium lauryl sulfate			Ph.Eur./ NF
Magnesium stearate [5]			Ph.Eur./ NF
(b) (4) Colloidal silicon dioxide			Ph.Eur./ NF
(b) (4)			Ph.Eur./ USP
Capsule fill weight			
Empty capsule shell, pre-printed			
Capsule shell (theoretical weight)[3]			Novartis monograph
Printing ink, black [4]			Table 2-3
Total capsule weight	**534.60**		
(b) (4)			

[3] The composition of the capsule shell is given in Table 2-2 below.
[4] The printing ink is a commercially available product composed of the ingredients shown in Table 2-3.

31a. **What is the proposed dissolution method? What data were provided to support the adequacy of the proposed dissolution method (e.g., medium, apparatus selection, etc.)?**

The Applicant selected USP Apparatus 2 (Paddle) and 0.1 M HCl as the dissolution medium. (b) (4)
Applicant investigated use of the following (b) (4) (b) (4), SDS, (b) (4) in 0.1M HCl, (b) (4) Paddle speeds of (b) (4) 75 rpm were also investigated. (b) (4)

Based on assessment of the generated experimental data, the Applicant selected the following dissolution testing conditions:

Apparatus:	USP 2 (Paddle)
Medium I:	1% SDS in 900 mL 0.1M HCl
Medium II:	1% SDS in 900 mL 0.1M HCl + Pepsin (2-Tier for stability samples)
Temperature:	37 (b) (4) °C
Rotation speed:	75 (b) (4) rpm

Sampling Times	15, 30, 45, 60, 90 min
Analysis:	HPLC-UV (λ = (b) (4))

Representative dissolution profiles of two scaled-up batches of Somidegib are shown in Figure 31-1.

Figure 31-1: Dissolution profiles of two scaled-up batches of Sonidegib Capsules at release [USP 2, 900 mL 1% SDS in 0.1M HCl, 75 rpm]

31b. What data are available to support the discriminating power of the method?

The Applicant investigated the discriminating Power of the dissolution method by evaluating the impact of sonidegib particle size on dissolution rate. (b) (4)

In the Applicant's response (dated 1/9/2015) to the Biopharmaceutics IR's in the 74-day letter, an additional experiment was conducted to investigate the discriminating power of the dissolution method by varying the quantity of (b) (4)

(b) (4)

Reviewer's Comments:

- (b) (4)
- *Although the Applicant has not rigorously investigated the discriminating ability of the proposed dissolution method, the method is deemed acceptable for QC purposes.*

31c. What information is available to support the robustness (e.g. linearity, accuracy, etc.) of the dissolution methodology?

The dissolution method for Sonidegib Capsules was validated using the drug product, reference drug substance, empty hard gelatin capsule shells, and placebo blend in capsules. The analytical UV method for quantitation of sonidegib in dissolution samples was validated for specificity, precision, linearity, accuracy, solution stability, and robustness parameters. The validation acceptance criteria were met and the method validation results are acceptable (see Table 6). Further details can be found in section 3.2.P.5.3, report # VR50111-1A (AS2459.

31d. Is the proposed dissolution/release method biorelevant? What data are available to support this claim?

(b) (4)

31e. Is the proposed dissolution method acceptable? If not, what are the deficiencies?

Yes, the dissolution method is acceptable.

31f. What are the proposed dissolution acceptance criteria for this product?

The Applicant has proposed two sampling time points (b) (4) The proposed dissolution acceptance criteria are:

Proposed Dissolution Acceptance Criteria	
Tier 1: Q = (b)(4)% in 30 min Q = % in 90 min	**Tier 2:** Q = (b)(4)% at 30 min Q = % at 90 min

31g. What data are available to support these criteria?

The Applicant submitted more detailed (b)(4) data, in response to IR comments, to justify the proposed dissolution acceptance criteria. Data for three registration batches (X1590812, X3310813, & X3320813) at release and at the 3, 6, and 12-month long-term stability time points were submitted on Jan 9, 2015; a summary of the data are provided in Tables 31-3 to 31-6. In the batch analyses section, dissolution data at release are provided for one clinical batch (X2780613) at 60 min (mean = (b)(4)%; range = (b)(4)%) and 90 min only (mean = (b)(4)%; range = (b)(4)%).

Table 31-3: Summary of dissolution profile data (Tier 1) at release for 3 registration/stability batches of Sonidegib Capsules, 200 mg (from page 12, section 3.2.P.5.6)

Analysis	Proposed specification	Batch X159 0812	Batch X331 0813	Batch X332 0813
Dissolution in 15 min [%] Mean (n) [Min – Max]		(b)(4)		
Dissolution in 30 min [%] Mean (n) [Min – Max]	Q = (b)(4)%			
Dissolution in 45 min [%] Mean (n) [Min – Max]				
Dissolution in 60 min [%] Mean (n) [Min – Max]				
Dissolution in 90 min [%] Mean (n) [Min – Max]	Q = (b)(4)%			

Table 31-4: Summary of dissolution profile data at 3 months for 2 registration/stability batches of Sonidegib Capsules, 200 mg (from page 15, section 3.2.P.5.6)

Batch Storage Packaging	Dissolution [%] Mean (n) [Min – Max] 15 min	30 min	45 min	60 min	90 min
Proposed specification for stability testing		Q = (b)(4)%			Q = (b)(4)%
Batch X159 0812 3 months storage at 25°C/60%RH (b)(4) blisters	(b)(4)				(b)(4)
Batch X331 0813 3 months storage at 25°C/60%RH HDPE bottle (90 mL/30 count)	(b)(4)				
Batch X332 0813 3 months storage at 25°C/60%RH HDPE bottle (90 mL/30 count)					

Table 31-5: Summary of dissolution profile data at 6 months for 2 registration/stability batches of Sonidegib Capsules, 200 mg (from page 15, section 3.2.P.5.6)

Batch Storage Packaging	Dissolution [%] Mean (n) [Min – Max] 15 min	30 min	45 min	60 min	90 min
Proposed specification for stability testing		Q = (b) (4)%			Q = (b) (4)%
Batch X159 0812 6 months storage at 25°C/60%RH (b) (4) blisters					(b) (4)
Batch X331 0813 6 months storage at 25°C/60%RH HDPE bottle (90 mL/30 count)					
Batch X332 0813 6 months storage at 25°C/60%RH HDPE bottle (90 mL/30 count)					

Table 31-6: Summary of dissolution profile data at 9 & 12 months for 1 registration/stability batche of Sonidegib Capsules, 200 mg (from pages 22 & 24 , section 3.2.P.5.6)

Batch Storage Packaging	Dissolution [%] Mean (n) [Min – Max] 15 min	30 min	45 min	60 min	90 min
Proposed specification for stability testing		Q = (b) (4)%			Q = (b) (4)%
Batch X159 0812 9 months storage at 25°C/60%RH (b) (4) blisters					(b) (4)
Batch X159 0812 12 months storage at 25°C/60%RH (b) (4) blisters					

31h. Are the proposed acceptance criteria adequate? If not, what are the recommended criteria? Is the setting of the dissolution acceptance criteria based on data from clinical and registration batches?

No, the proposed dissolution acceptance criteria are not adequate. This Reviewer recommend that a single set of dissolution specification time points should be used for purposes of quality control at release and during stability.

Table 31-3 displays the dissolution profiles of the three registration batches (X1590812, X3310813, & X3320813) at release; based on these data, the grand mean of percent sonidegib dissolved at 30 min is (b) (4)% (range (b) (4) %).

It should be mentioned that the dissolution profile data for the clinical batches were not submitted to the NDA. Therefore, the following IR was sent to the Applicant to submit dissolution profile data for the clinical batches in order to adequately evaluate the acceptance criteria:

Biopharmaceutics Information Request (sent 3/25/2015):
Provide the dissolution profile data at release for the clinical batches of Sonidegib Capsules, 200 mg, used in the Phase II safety and efficacy study (# A2201). For each clinical batch, state the duration of use in the study. In addition, submit the stability dissolution profile data generated for the four clinical batches in support of their use in Study A2201. In order to facilitate review of the requested data, provide the overall mean of percent sonidegib dissolved at each time point and the associated overall range across all clinical batches. Please use the following Table to provide the dissolution data.

	% Sonidegib Dissolved Mean(n), [range], %CV				
Batch Number	**15 min**	**30 min**	**45 min**	**60 min**	**90 min**
X280 1110					
X076 0211					
X193 0711					
X278 0613					
Grand Mean **Overall Range**					

Applicant's Response to the IR:

The Applicant submitted responses to the IR on 3/30/2015 (Sequence # 0031). Based on the submitted dissolution profile data for the clinical batches, this Reviewer recommends the following dissolution acceptance criteria for Sonidegib Capsules, 200 mg, at release and on stability:

Recommended Dissolution Acceptance Criteria	
Tier 1: Q = (b)(4)% in 30 min Q = % in 90 min	**Tier 2:** Q = (b)(4)% in 30 min Q = % in 90 min

Biopharmaceutics Information Request (sent 4/7/2015):
Based on the provided dissolution data for the clinical batches used in Study CLDE225A2201, the dissolution acceptance criteria for Sonidegib Capsules, 200 mg, the FDA-recommended dissolution acceptance criteria during Tier-1 and Tier 2 testing are:

30 min: NLT (b)(4)%
90 min: NLT %

Implement the recommended dissolution acceptance criteria and submit an updated Specifications Table to the NDA by 4/13/2015.

Following a teleconference on 4/16/2015, the following agreed-upon dissolution acceptance criteria were added to the Specifications Table on 4/17/2015:

Q = (b)(4)% in 30 min
Q = % in 90 min

33. **Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial drug product?**

The Applicant's proposed commercial drug product is identical to the drug product used in the clinical trials. Bridging of the clinical and commercial products is therefore not applicable to this NDA.

Reviewer's Assessment:

Drug Substance: (b) (4) (b) (4)

BCS: (b) (4) (b) (4)

Drug Product: The proposed drug product for commercialization is a hard gelatin capsule formulation containing 200 mg of sonidegib. (b) (4) (b) (4)

Clinical Information: One pivotal safety and efficacy study (# CLDE225A2201) in 230 patients was conducted in support of the clinical basis for approval of this NDA. Several clinical pharmacology studies were also conducted in healthy volunteers and in patients; a number of these studies were ongoing at the time of NDA filing. Briefly, sonidegib exhibits poor absolute bioavailability of 6 – 14 % with a median T_{max} after oral administration of 2- 4 h. High-fat meal increases sonidegib systemic exposure 7.4-fold. The pharmacokinetics of sodidegib are linear over the dose range of 100 – 400 mg; above 400 mg, the systemic exposure increases less than proportionally with dose. The drug is 97% bound to plasma proteins and is extensively metabolized to pharmacologically inactive compounds. The estimated half-life of sonidegib is 28 days, with steady state attained after 4 months of treatment. Parent sonidegib and metabolites are excreted almost exclusively in feces; only 1.95% of total radioactivity is recovered in urine.

Review: The Biopharmaceutics review was focused on the evaluation and acceptability of the following:

- Adequacy of the dissolution method;
- Adequacy of the proposed dissolution acceptance criterion;
- Confirmation that no formulation bridging is needed.

*Reviewer's Assessment - Dissolution Method and Acceptance Criteria:*The Applicant's proposed dissolution method for Sonidegib Capsules, 200 mg, is acceptable; however, the proposed acceptance criteria are not acceptable.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Recommendation and Signature:

The Division of Biopharmaceutics recommends **APPROVAL** of NDA 205266 for Sonidegib Capsules, 200 mg.

The dissolution method and acceptance criteria for the QC release and stability testing of Sonidegib Capsules, 200 mg, agreed between FDA and the Applicant are as follows :

Apparatus/RPM	Medium/Volume/Temperature	Acceptance Criteria
USP Apparatus 2/ 75 rpm	**Tier 1:** 900 ml of 1% SDS in 0.1M HCl at 37°C **Tier 2:** 900 ml of 1% SDS in 0.1M HCl + Pepsin at 37°C	**Tier 1/Tier 2:** Q = (b) (4)% in 30 min Q = % in 90 min

Signature Block

Angelica Dorantes -S

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Date: 2015.05.15 11:34:22 -04'00'

Okpo Eradiri, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics, OPQ

Supervisor Comments and Concurrence:

I concur with Dr. Eradiri's Biopharmaceutics assessment and recommendation.

Angelica Dorantes -S

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Date: 2015.05.15 11:32:08 -04'00'

Angelica Dorantes, Ph.D.
Acting Biopharmaceutics Branch Chief
Division of Biopharmaceutics, OPQ

Note: additional reviewers can be added, as appropriate

ASSESSMENT OF MICROBIOLOGY

34. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

The microbial limits specification for ODOMZO® (Sonidegib) capsules is acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.

ODOMZO® is a capsule for oral administration.

The drug product is tested for microbial limits at release using a method consistent with USP Chapter <61> (Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests) and <62> (Microbiological Examination of Non-sterile Products: Tests for Specified Microorganisms). The microbial limits acceptance criteria are consistent with USP Chapter <1111> (Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use).

The microbial Limits test methods were verified to be appropriate for use with the drug product following procedures consistent with those in USP Chapter <61> and <62>. The microbial limits specification is provided in the table below:

Test	Limit	Test Methodology
Total Aerobic Microbial Count	NMT 10^3 CFU/g	USP <61>
Total Yeasts and Molds Count	NMT 10^2 CFU/g	USP <61>
Escherichia coli	Absence in 1g	USP <62>

The drug product will also be tested for microbial limits annually as part of the post-approval stability protocol.

ADEQUATE

Applicant's Response: Not applicable

Reviewer's Assessment: The microbiological quality of the drug product is controlled via a suitable testing protocol.

2.3.P.6 Reference Standards or Materials

35. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Because the drug product is not sterile, the container closure system does not need to function as a barrier to microbial ingress.

Reviewer's Assessment: The container closure system is suitable for a non-sterile drug product.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

The materials used for the manufacture of the drug product do not present a significant risk of adventitious agent contamination.

Reviewer's Assessment: There is a minimal risk of adventitious agent contamination of the finished drug product.

Reviewer's Assessment:

There is a minimal risk of adventitious agent contamination in the finished drug product.

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:

QUALITY ASSESSMENT
NDA # 205266

Stephen E. Langille -S

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Supervisor Comments and Concurrence:

Bryan S. Riley -S

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Date: 2015.05.15 13:45:58 -04'00'

Note: additional reviewers can be added, as appropriate

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

ODOMZO® (sonidegib) capsules for oral use
Initial U.S. Approval: XXXX

DOSAGE AND ADMINISTRATION
The recommended dose is 200 mg orally once daily (2)

(b) (4)

DOSAGE FORMS AND STRENGTHS
200 mg capsules (3)

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name		Acceptable based on MAPP 5021.1
Dosage form, route of administration		Acceptable
Controlled drug substance symbol (if applicable)		N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths		Acceptable

Conclusion: Submission states that recommended dose is 200mg/day (b) (4) (section 7.1), (b) (4) the 200mg dose will be prescribed, thus the MDD is 200mg.

(b) "Full Prescribing Information" Section

Section 2: DOSAGE AND ADMINISTRATION
The recommended dosage of ODOMZO is 200 mg taken orally once daily, (b) (4)
(b) (4)

Section 3. DOSAGE FORMS AND STRENGTHS
(b) (4) 200 mg opaque pink capsules with 'SONIDEGIB 200MG' printed on the body and 'NVR' printed on the cap in black ink.

Section 11: DESCRIPTION
Sonidegib is aSmoothened (Smo) antagonist which inhibits the Hedgehog (Hh) signaling pathway.

The molecular formula for sonidegib diphosphate is $C_{26}H_{26}F_3N_3O_3 \cdot 2H_3PO_4$. The molecular weight is 681.49 daltons. The chemical name is N-[6-(cis-2,6-dDimethylmorpholin-4-yl)pyridine-3-yl]-2-methyl-4'-(trifluoromethoxy) [1,1'-biphenyl]-3-carboxamide diphosphate.

The molecular structure is shown below:

[molecular stucture]

Sonidegib (b) (4) phosphate is a white to off-white powder.

Sonidegib free base is practically insoluble (b) (4) (b) (4)

Each ODOMZO capsule contains 200 mg of sonidegib as the free base and the following inactive ingredients: colloidal silicon dioxide, crospovidone, lactose monohydrate, magnesium stearate, poloxamer and sodium lauryl sulfate. The opaque pink hard gelatin capsule shell contains gelatin, red iron oxide, and titanium dioxide. The black printing ink contains ammonium hydroxide, iron oxide black, propylene glycol, and shellac.

Section 16: HOW SUPPLIED/STORAGE AND HANDLING
Each ODOMZO capsule has an opaque pink color with 'SONIDEGIB 200MG' printed on the capsule body and 'NVR' printed on the cap in black ink. ODOMZO capsules are supplied as follows:
Bottle of 30 capsules NDC 0078-0645-15
Unit dose package of 30 capsules) NDC 0078-0645-30
(b) (4) 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). (b) (4)

(b) (4)

MEDICATION GUIDE
ODOMZO® (o-DOM-zo)
sonidegib
capsules

How (b) (4) I store ODOMZO?
(b) (4)
Store ODOMZO at room temperature (77°F, 25°C); (b) (4)
Keep ODOMZO and all medicines out of the reach of children.

What are the ingredients in ODOMZO?
Active ingredient: sonidegib
Inactive ingredients: colloidal silicon dioxide, crospovidone, lactose monohydrate, magnesium stearate, poloxamer, and sodium lauryl sulfate. The capsule shell contains

gelatin, red iron oxide, and titanium dioxide. The black printing ink contains ammonium hydroxide, black iron oxide, propylene glycol, and shellac.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

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T201X-XX/T201X-XX
Month Year/Month Year

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms		Acceptable
Strengths: in metric system		Acceptable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.		Acceptable

Conclusion: Information is acceptable

#11: Description (21CFR 201.57(c)(12))

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name		Acceptable
Dosage form and route of administration		Acceptable
Active moiety expression of strength with equivalence statement for salt (if applicable)		Acceptable
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.		N/A
Statement of being sterile (if applicable)		Acceptable
Pharmacological/ therapeutic class		Acceptable
Chemical name, structural formula, molecular weight		Acceptable
If radioactive, statement of important nuclear characteristics.		N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)		N/A

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form		Acceptable
Available units (e.g., bottles of 100 tablets)		(b) (4)
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number		Acceptable
Special handling (e.g., protect from light, do not freeze)		Acceptable
Storage conditions		Acceptable

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)		Acceptable

Conclusion:

Grammatical revisions as indicated.

Section 2: (b) (4) Editorial additions and are indicated.

Medication Guide: CMC information is acceptable.

2. Labels

Amendment S-047

1) Immediate Container Label

(b) (4)

(b) (4)

[redacted]

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	API is not a salt	Acceptable
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		Acceptable
Net contents (21 CFR 201.51(a))		Acceptable
Lot number per 21 CFR 201.18		Acceptable
Expiration date per 21 CFR 201.17		Acceptable
"Rx only" statement per 21 CFR 201.100(b)(1)		Acceptable
Storage (not required)	Storage conditions are listed.	Acceptable
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		Acceptable
Bar Code per 21 CFR 201.25(c)(2)**		Acceptable
Name of manufacturer/distributor		Acceptable
Others	Statement "product of Switzerland" is accepted (needed to satisfy a US Customs requirement).	Acceptable

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Blister Label: (b) (4)

(b) (4)

2) Cartons

Amendment S-047

(b) (4)

Appears this way on original

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))		Acceptable
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		Acceptable
Net contents (21 CFR 201.51(a))	The labels should include an equivalency statement on the side panels such as "Each capsule contains 200 mg sonidegib (equivalent to XXX.X mg sonidegib diphosphate."	
Lot number per 21 CFR 201.18		Acceptable
Expiration date per 21 CFR 201.17		Acceptable
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]		Acceptable
Sterility Information (if applicable)		**N/A**
"Rx only" statement per 21 CFR 201.100(b)(1)		Acceptable
Storage Conditions	Supported by the stability protocols and study data.	Acceptable
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		Acceptable
Bar Code per 21 CFR 201.25(c)(2)**		Acceptable
Name of manufacturer/distributor		Acceptable
"See package insert for dosage information" (21 CFR 201.55)		Acceptable
"Keep out of reach of children" (optional for Rx, required for OTC)		Acceptable
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))		N/A

Conclusion: Absence of a carton label is acceptable to DMEPA. Statement "product of Switzerland" is accepted (needed to satisfy a US Customs requirement)

Environmental Assessment

The applicant claims a categorically exclusion from the requirement to prepare an Environmental Assessment (EA) under 21 CFR Part 25.31(b) in that the estimated concentration of the substance at the point of entry into the aquatic environment will be less than 1 part per billion (ppb) based on the peak production estimates over the next five years.

Year	*2013*	*2014*	*2015*	*2016*	*2017*	*2018*
Estimated Production Total API (kg)						(b) (4)

Expected Introduction Concentration (EIC) – Aquatic calculation:

EIC = (A)(B)(C)(D) = (b) (4) µg/L = (b) (4) ppb

where:

A = peak kg/year produced for direct use (as active moiety)

B = $1/(1.218 \times 10^{11}$ liters/day) entering POTWs per 1996 Clean Water Needs Survey

C = 1 year/365 days per year

D = 10^9 µg/kg (conversion factor)

II. List of Deficiencies To Be Communicated

A. Drug Substance
B. Drug Product
C. Process/Facility
D. Biopharmaceutics
E. Microbiology
F. Label/Labeling

III. Attachments

A. Facility

OVERALL RECOMMENDATION:				
DRUG SUBSTANCE				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION
DRUG PRODUCT				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION

B. Lifecycle Knowledge Management

a) Drug Substance

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Initial Risk Ranking*	Justification	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments**
	H, M, or L			Acceptable or Not Acceptable	

b) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking*	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments**
		H, M, or L		Acceptable or Not Acceptable	

*Risk ranking applies to product attribute/CQA

**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.

IV. Administrative

A. Reviewer's Signature

B. Endorsement Block

Reviewer Name/Date: William Adams
Secondary Reviewer Name/Date: Olen Stephens
Project Manager Name/Date: Teicher Agosto