

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205858Orig1s000**

**CHEMISTRY REVIEW(S)**

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

**Application:** NDA 205858/000  
**Org. Code:** 161  
**Priority:** 1Y  
**Stamp Date:** 11-SEP-2013  
**PDUFA Date:** 11-SEP-2014  
**Action Goal:**  
**District Goal:** 11-APR-2014

**Sponsor:** GILEAD SCIENCES INC  
 199 EAST BLAINE ST  
 SEATTLE, WA 98102  
**Brand Name:** IDELALISIB (GS-1101)  
**Estab. Name:**  
**Generic Name:** IDELALISIB (GS-1101)  
**Product Number; Dosage Form; Ingredient; Strengths**  
 001; TABLET; IDELALISIB; 100MG  
 002; TABLET; IDELALISIB; 150MG

<b>FDA Contacts:</b>	D. GHOSH	Prod Qual Reviewer	(HFD-150)	3017964093
	J. COLE	Micro Reviewer		3017965148
	J. MARTIN	Product Quality PM	(HFV-530)	3017962072
	M. MILLER	Regulatory Project Mgr		3017960683
	J. BROWN	Team Leader		3017961652

**Overall Recommendation:** ACCEPTABLE on 17-MAY-2014 by R. XU ( ) 3017966187  
 PENDING on 24-JAN-2014 by EES\_PROD

**Establishment:** CFN: (b) (4) FEI: (b) (4)  
 (b) (4)

**Address:** AADA:

**Responsibilities:** DRUG SUBSTANCE STABILITY TESTER  
 FINISHED DOSAGE RELEASE TESTER  
 FINISHED DOSAGE STABILITY TESTER

**Profile:** CONTROL TESTING LABORATORY **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 23-DEC-2013

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

**Establishment:** CFN: (b) (4) FEI: (b) (4)  
(b) (4)

**DMF No:** AADA:

**Responsibilities:** DRUG SUBSTANCE RELEASE TESTER

**Profile:** CONTROL TESTING LABORATORY OAI Status: NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 01-OCT-2013

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

---

**Establishment:** CFN: 9615378 FEI: 3001027806  
GILEAD ALBERTA ULC  
1021 HAYTER RD NW  
EDMONTON, ALBERTA, CANADA

**DMF No:** AADA:

**Responsibilities:** DRUG SUBSTANCE MANUFACTURER

**Profile:** NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 17-MAY-2014

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

---

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

**Establishment:** **CFN:** 3006709727 **FEI:** 3006709727  
GILEAD SCIENCES LIMITED  
IDA BUSINESS & TECHNOLOGY PARK  
CARRIGTOHILL, CO. CORK, IRELAND

**DMF No:** **AADA:**

**Responsibilities:** FINISHED DOSAGE LABELER  
FINISHED DOSAGE PACKAGER  
FINISHED DOSAGE RELEASE TESTER

**Profile:** CONTROL TESTING LABORATORY **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 30-JAN-2014

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

**Profile:** TABLETS, PROMPT RELEASE **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 25-FEB-2014

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

---

**Establishment:** **CFN:** 2082946 **FEI:** 2082946  
GILEAD SCIENCES, INC.  
SAN DIMAS, , UNITED STATES 917732957

**DMF No:** **AADA:**

**Responsibilities:** FINISHED DOSAGE LABELER  
FINISHED DOSAGE PACKAGER

**Profile:** TABLETS, PROMPT RELEASE **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 09-OCT-2013

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

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**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

**Establishment:** CFN: (b) (4) FEI: (b) (4)  
(b) (4)

**DMF No:** AADA:

**Responsibilities:** FINISHED DOSAGE RELEASE TESTER  
FINISHED DOSAGE STABILITY TESTER

**Profile:** CONTROL TESTING LABORATORY **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 27-DEC-2013

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

---

**Establishment:** CFN: (b) (4) FEI: (b) (4)  
(b) (4)

**DMF No:** AADA:

**Responsibilities:** FINISHED DOSAGE LABELER  
FINISHED DOSAGE MANUFACTURER  
FINISHED DOSAGE PACKAGER

**Profile:** TABLETS, PROMPT RELEASE **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 29-OCT-2013

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

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/s/  
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SHANNON J CREWS  
07/28/2014

## Zydelig (idelalisib) Tablets

NDA 205858/206545

### Summary Basis for Recommended Action from Chemistry, Manufacturing, and Controls

**Applicant:** Gilead Sciences, Inc.,  
199 East Blaine Street  
Seattle  
WA98102

**Indication:** NDA 205858: For the treatment of patients with refractory indolent non-Hodgkin lymphoma (iNHL).

NDA 206545: For the treatment of patients with chronic lymphocytic leukemia (CLL)

**Presentation:** The product will be available as 100 mg (orange colored) and 150 mg (pink colored), oval-shaped, film-coated tablets, debossed with “GSI” on one side and “100” or “150” on the other side, respectively. The tablets are packaged as 60-count in 60 ml, white, high density polyethylene (HDPE) bottles with a polyester fiber coil and child-resistant (b) (4) screw cap with an (b) (4) foil liner.

**EER Status:** Overall recommendation is pending as of 12-May-2014.

**Consults:** ONDQA Biopharmaceutics - Acceptable (Sandra Suarez, 9-May-2014).

Microbiology - Acceptable (Jessica Cole, 2-Jan-2014)

Methods Validation – Submitted to FDA labs, results are pending

EA – Categorical exclusion granted.

Post-Approval Agreements: None

### Drug Substance:

The drug substance, idelalisib, a new molecular entity, is a (b) (4) substance. It is a white to almost white (b) (4) substance. Idelalisib is designated as a BCS class II with low solubility and high permeability. Idelalisib can exist in two (b) (4) forms, Form I and Form II. (b) (4) is manufactured consistently and used for the manufacture of the drug product. (b) (4)

Stability data has been provided which demonstrate that there is no (b) (4) on storage. Both forms have comparable solubility and other relevant physical properties. Because of no (b) (4) and comparable solubility, the risk of product failure based on drug substance polymorphic form is acceptable. The drug substance synthesis is a (b) (4) synthesis. The structure of the drug substance was adequately established using appropriate analytical techniques.

The drug substance quality is ensured through quality control of all starting materials, in-process controls throughout the manufacturing process, appropriate quality control of the isolated intermediates and the appropriate final drug substance specification. The drug substance specification includes tests and acceptance criteria for drug substance critical quality attributes, e.g., identification, assay, impurities, enantiomeric purity, particle size distribution, residual solvents, and elemental impurities. The analytical procedures have been adequately described and validated to control the quality of the drug substance. The stability of the drug substance has been demonstrated through appropriate stability studies to support a retest period of (b) (4) months when stored (b) (4) (b) (4).

### Drug product:

Zydelig (idelalisib) tablets are an immediate release product to be marketed as 100 mg and 150 mg strengths. The drug product formulation uses standard compendial excipients. These are microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, sodium starch glycolate, and magnesium stearate. The manufacturing process includes (b) (4) (b) (4). The manufacturing process has appropriate in-process controls to ensure the quality of the drug product. The product quality is further ensured through end product testing. The end product specification includes testing for appearance, identification, assay, (b) (4) uniformity of dosage units, degradation products, dissolution, and microbial controls. All analytical procedures for the drug product are adequately described and validated. An expiration period of 24 months is granted for the product.

The drug product is stored at 25°C with excursions permitted 15-30°C (59-86°F).

**Conclusion:** Adequate from CMC perspective.

**Additional Items:**

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application. Although the method validation of analytical procedures by the FDA laboratory is not complete at this point, it is not an approvability issue.

**Overall Conclusion:** An overall recommendation for the manufacturing facilities from the Office of Compliance is pending at this point. All other CMC related issues have been resolved. A final recommendation for the approval of the application will be put into DARRTS by the CMC reviewer after the overall facility recommendation from the Office of Compliance.

Ramesh K. Sood, Ph.D.  
Acting Director, DPA I/ONDQA

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/s/  
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RAMESH K SOOD  
05/13/2014

**NDA 205858**

**NDA 206545**

**ZYDELIG™ (idelalisib) Tablets**

**Gilead Sciences, Inc.**

**Debasis Ghosh, Ph.D., M. Pharm.**

*(drug substance reviewer)*

**Li Shan Hsieh, Ph.D.**

*(drug product reviewer)*

**Office of New Drug Quality Assessment  
Division of New Drug Quality Assessment I  
Branch II**

**CMC REVIEW OF NDA 205858 and NDA 206545  
For the Office of Hematology and Oncology Products  
Division of Hematology Products**

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CMC Review Data Sheet

# CMC Review Data Sheet

1. NDA 205858 and NDA 206545
2. REVIEW #: 1
3. REVIEW DATE: 10-May-2014
4. REVIEWERS: Dr. Debasis Ghosh and Dr. Li Shan Hsieh
5. PREVIOUS DOCUMENTS:

Previous Documents

Original IND 101254 submission (SD 003)

Document Date

02-May-2008

6. SUBMISSION(S) BEING REVIEWED:

NDA 205858

Submission(s) Reviewed	eCTD Sequence No.	DARRTS SD Number	Document Date	Stamp Date
Original NDA Submission	0000	0001	11-Sep-2013	13-Sep-2013
Amendment (Quality)	0013	0014	16-Dec-2013	17-Dec-2013
Amendment (Quality)	0023	0024	28-Jan-2014	28-Jan-2014
Amendment (Quality)	0030	0031	12-Mar-2014	12-Mar-2014
Amendment (Quality)	0032	0033	21-Mar-2014	21-Mar-2014
Amendment (Quality)	0033	0034	24-Mar-2014	24-Mar-2014
Amendment (Quality)	0034	0035	31-Mar-2014	29-Mar-2014
Amendment (Quality)	0037	0038	14-Apr-2014	14-Apr-2014
Amendment (Quality)	0042	0043	08-May-2014	08-May-2014

NDA 206545

Submission(s) Reviewed	eCTD Sequence No.	DARRTS SD Number	Document Date	Stamp Date
Original NDA Submission	0001	0002	06-Dec-2013	06-Dec-2013
Amendment (Quality)	0007	0008	28-Jan-2014	28-Jan-2014
Amendment (Quality)	0008	0009	31-Jan-2014	31-Jan-2014
Amendment (Quality)	0013	0014	21-Mar-2014	21-Mar-2014
Amendment (Quality)	0014	0015	24-Mar-2014	24-Mar-2014
Amendment (Quality)	0017	0018	07-Apr-2014	07-Apr-2014
Amendment (Quality)	0022	0023	08-May-2014	08-May-2014

## CMC Review Data Sheet

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: Gilead Sciences Inc.  
Address: 199 East Blaine Street  
Representative: Seattle, Washington 98102  
Telephone: (206) 832-2049

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: ZYDELIG™  
b) Non-Proprietary Name: Idelalisib  
c) Code Name/# (ONDQA only): NA  
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: I, New Molecular Entity
  - Review Priority: Standard
  - Breakthrough Therapy Designation: No

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

10. PHARMACOL. CATEGORY: Inhibitor of phosphatidylinositol-3  
kinase p110 $\delta$  (PI3K $\delta$ )

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 100 mg and 150 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

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

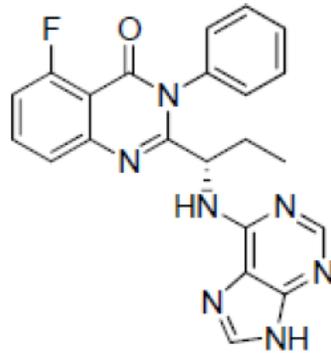
IUPAC: 5-Fluoro-3-phenyl-2-[(1S)-1-(9H-purin-6-ylamino)propyl]quinazolin-4(3H)-one  
CAS: 4(3H)-Quinazolinone, 5-fluoro-3-phenyl-2-[(1S)-1-(9H-purin-6-ylamino)propyl]-

CMC Review Data Sheet

Empirical Formula: C<sub>22</sub>H<sub>18</sub>FN<sub>7</sub>O

Formula Weight: 415.42

Chemical Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF # (b) (4)	TYPE	HOLDER	ITEM REFERENCED (b) (4)	CODE <sup>1</sup>	STATUS <sup>2</sup>	LoA date
	III			4		19-Jul-2013
	III			4		22-Jul-2013
	III			4		13-May-2011
	III			4		22-Jul-2013
	III			4		11-Jun-2013
	IV			4		24-Jul-2013

<sup>1</sup> Acti

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")

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

CMC Review Data Sheet

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	101254	Change of ownership

18. STATUS:

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER(S)
Biometrics	Indicate for the treatment	09-May-2014	Kyung Y Lee
EES	Pending		
Pharm/Tox	“Recommended for the proposed indication”	03-Apr-2014	Natalie Simpson Ramadevi Gudi
Biopharm	“Recommended for approval”	09-May-2014	Sandra Suarez
LNC	N/A		
Methods Validation	Pending		
DMEPA*	Acceptable	19-Sep-2013	
EA	Adequate	09-May-2014	Li Shan Hsieh
Microbiology	“Recommended for approval”	02-Jan-2014	Jessica Cole
CDRH Consult	N/A		

\*DMEPA: Division of Medication Error Prevention and Analysis

## Executive Summary Section

# The CMC Review for NDA 205858 and NDA 206545

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The application is considered Adequate for Chemistry Manufacturing and Control – drug substance and drug product - in that complete and acceptable data and information has been submitted. The CMC review team recommends that the application be Approved pending overall recommendation from the Office of Compliance.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

### II. Summary of CMC Assessments

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

##### (1) Drug Substance

The drug substance, idelalisib, is a (b) (4) (b) (4) It is a white to off-white, (b) (4). The aqueous solubility of idelalisib is pH dependent. It is soluble in acidic pH and insoluble in basic pH. Based on the cell permeability study, idelalisib is designated as BCS Class II (low solubility, high permeability).

The chemical structure of idelalisib is confirmed by (b) (4) infra-red spectroscopy, nuclear magnetic resonance spectroscopy, high resolution mass spectroscopy, elemental analysis, and ultraviolet absorption spectroscopy.

Polymorphism is one of the critical quality attributes for immediate release tablets. Idelalisib exhibits polymorphism. Two (b) (4) forms are Form I and Form II. Both forms are similar with respect to solubility and other physical properties. (b) (4) is manufactured consistently using the proposed manufacturing method. (b) (4) Stability data demonstrated that (b) (4) during the proposed storage conditions. Since both forms (I and II) are equivalent, the risk of failure of drug product (immediate release oral tablet) due to (b) (4) is low.

## Executive Summary Section

Idelalisib is synthesized from a (b) (4). The material attributes of the starting materials are controlled by specifications. The reaction intermediates are also (b) (4). The description of the manufacturing process includes normal operating range (NOR) for each process parameter. However, proven acceptable range (PAR) for each process is included for information purposes only. The applicant committed to implement NOR only. Any change of NOR will be reported to the Agency. The final drug substance is (b) (4).

(b) (4) The specifications of other critical quality attributes including assay and impurities are adequately justified. The analytical method for each critical quality attribute is provided. The validation report for all non-compendial methods are also provided.

The drug substance is subjected to long-term (25°C/60%RH) and accelerated (40°C/75%RH) conditions. No changes of purity and impurity contents have been observed in any of the drug substance batches tested during 36 months period for long-term and 6 months period for accelerated stability. Stress studies are carried out at -20°C to 60°C at ambient humidity for 4 weeks. Photostability study is performed as per ICHQ1B. Stability is demonstrated on idelalisib samples that have been stored at -20°C, 5°C, and 60°C/ambient humidity for 4 weeks. Idelalisib was demonstrated to be stable even after exposing to (b) (4) (b) (4) for up to (b) (4). Idelalisib is not photolabile, and therefore the drug substance does not require special protection against light exposure. The applicant proposed a retest period of (b) (4) months when stored at the recommended storage condition (Store at (b) (4)). The proposed retest period may be granted. The applicant provided a post-approval commitment to continue stability study with commercial batches.

## (2) Drug Product

Zydelig (idelalisib) tablets, 100 mg (orange color) and 150 mg (pink color), are oval-shaped, film-coated tablets, debossed with "GSI" on one side, "100" and "150" on the other side, respectively.

The core inactive excipients ingredients are microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, sodium starch glycolate, and magnesium stearate. The tablets are film-coated with a material containing the following inactive ingredients: red iron oxide (150 mg), FD&C Yellow #6/Sunset Yellow FCF Aluminum Lake (100 mg), polyethylene glycol, talc, polyvinyl alcohol, and titanium dioxide.

## Executive Summary Section

Zydelig tablets, 100 mg and 150 mg, are packaged in 60 mL, white, high density polyethylene (HDPE) bottles with a polyester fiber coil. Each bottle contains sixty (60) tablets and is capped using a white, continuous thread, child-resistant (b) (4) screw cap with an (b) (4) foil liner.

The manufacturing of Zydelig tablets involve the following steps: (b) (4)

(b) (4)

The quality of Zydelig film-coated tablets has been assessed based on its manufacturing process and process controls; the analytical procedures for identification, purity, strength, and stability. Based on the submitted stability data on stress and long term study, a 24 months expiry period has been accepted with storage at controlled room temperature.

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

NDA 205858:

The treatment of patients with refractory indolent non-Hodgkin lymphoma (iNHL).

NDA 206545:

The treatment of patients with chronic lymphocytic leukemia (CLL)

**C. Basis for Approvability or Not-Approval Recommendation**

The requirements of 21 CFR 314.50(d)(1) have been adequately met by the applicant.

All drug substance and drug product manufacturing, packaging and control facilities were submitted to EES. An overall recommendation is pending.

## Executive Summary Section

**III. Administrative****A. Reviewer's Signature:**

*(See appended electronic signature page)*

Debasis Ghosh, Ph.D., M. Pharm., ONDQA

Li Shan Hsieh, Ph.D., ONDQA

**B. Endorsement Block:**

*(See appended electronic signature page)*

Ali Al-Hakim, Ph.D., Branch Chief, Branch II, Division of New Drug Quality Assessment I (DNDQA I), ONDQA

**C. CC Block:** entered electronically in DARRTS

Janice Brown, M.S., CMC Lead, Branch II, Division of New Drug Quality Assessment I (DNDQA I), ONDQA

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/s/  
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DEBASIS GHOSH  
05/12/2014

LI SHAN HSIEH  
05/12/2014

ALI H AL HAKIM  
05/12/2014

# Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre- Marketing Applications (Original)

- I. Review Cover Sheet
- II. Application Detail
- III. Filing Checklist
- IV. Manufacturing Summary
- V. Overall Conclusions and Recommendations

## I. Review Cover Sheet

1. DMPQ Reviewer: **Vipul Dholakia**

2. NDA/BLA Number: **NDA 205-858**

Submission Date: **9/11/2013**

21<sup>st</sup> C. Review Goal Date: **07/11/2014**

PDUFA Goal Date: **09/11/2014**

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	(b) (4) <b>(Proposed)</b>
Established or Non-Proprietary Name (USAN) and strength:	<b>Idelalisib</b>
Dosage Form:	<b>Tablets</b>

4. SUBMISSION PROPERTIES:

Review Priority :	<b>STANDARD</b>
Applicant Name:	Gilead Science Inc.
Responsible Organization (OND Division):	DHP

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
For Pre-Marking Applications

## II. Application Detail

1. INDICATION: indolent non-Hodgkin lymphoma (iNHL))
2. ROUTE OF ADMINISTRATION: Oral
3. STRENGTH/POTENCY: 100 mg and 150 mg
4. Rx/OTC DISPENSED:   Rx       OTC
5. ELECTRONIC SUBMISSION (yes/no)? Yes
6. PRIORITY CONSIDERATIONS:

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V	X			
2.	Breakthrough Therapy Designation		X		
3.	Orphan Drug Designation		X		
4.	Unapproved New Drug		X		
5.	Medically Necessary Determination		X		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		X		
7.	Rolling Submission		X		
8.	Drug/device combination product with consult		X		
9.	Complex manufacturing		X		
10.	Other (e.g., expedited for an unlisted reason)		X		

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For Pre-Marking Applications

### III. FILING CHECKLIST

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

<b>A. COMPLETENESS OF FACILITY INFORMATION</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
11.	Is a single comprehensive list of all involved facilities available in one location in the application?	X		
12.	Is all site information complete (e.g., contact information, responsibilities, address)?	X		
13.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	X		
14.	Do all sites indicate they are ready to be inspected (on 356h)?	X		
15.	Additional notes (non-filing issue) 1. Are all sites registered or have FEI #? 2. Do comments in EES indicate a request to participate on inspection(s)? 3. Is this first application by the applicant?	X	X  X	

\*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQ. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

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<b>B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
16.	Have any Comparability Protocols been requested?		X	

<b>IMA CONCLUSION</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
17.	Does this application fit one of the EES Product Specific Categories?	X		NME
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion? Have all EERs been updated with final PAI recommendation?	X		
19.	<b>From a CGMP/facilities perspective, is the application fileable?</b>  If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	X		

## IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements?			
Nanotechnology <input type="checkbox"/>	RTRT Proposal <input type="checkbox"/>	PAT <input type="checkbox"/>	Drug/Device Combo <input type="checkbox"/>
PET <input type="checkbox"/>	Design Space <input type="checkbox"/>	Continuous Mfg <input type="checkbox"/>	Naturally derived API <input type="checkbox"/>
Other (explain):	<b>None</b>		

### Manufacturing Highlights

#### 1. Drug Substance

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	

#### 2. Drug Product

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	

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**3. Facility-Related Risks or Complexities (e.g., number of foreign sites, large number of sites involved, etc.)**

**Drug substance** is manufactured by Gilead Alberta, ULC, Canada and other testing laboratories are based in USA

**Drug Product** is manufactured by (b) (4) and other testing facilities and packaging sites are located in USA.

(b) (4)

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**Manufacturing Facilities Chart** (generated from 602A DARRTS report and OMPQ macro):

Establishment Name	FEI Num	District Short	Country Code	Responsibilities	Profile Code	Inspection History, Dates, Classifications	PAI Recommendation	Most Recent Milestone	Most Recent EER Compliance Status	Comment
GILEAD ALBERTA ULC	3001027806	AME	CAN	Drug substance manufacturing and release testing	CSN	10/22 - 25/2012 NAI 08/02 - 05/2011 NAI 03/23 - 26/2009 NAI	Submitted to DO for Inspection 9/25/2013	INSPECTION PERFORMED 3/3 - 7/2014	PN	Inspection report under review
(b) (4)				Drug substance and drug product release and stability testing	CTL	(b) (4) NAI NAI NAI	Submitted to DO for Inspection (b) (4)	OC RECOMMENDATION	AC	Based on profile and DO recommendation. Reevaluation in (b) (4) (b) (4)
(b) (4)				Drug substance release testing	CTL	(b) (4) NAI NAI NAI	10 day letter submitted to DO (b) (4)	OC RECOMMENDATION	AC	Based on profile and DO recommendation. Reevaluation in (b) (4) (b) (4)
(b) (4)				Drug product release and stability testing	CTL	(b) (4) NAI NAI AI	Submitted to DO for Inspection (b) (4)	OC RECOMMENDATION	AC	Based on profile and DO recommendation. Reevaluation in (b) (4) (b) (4)
GILEAD SCIENCES LIMITED	3006709727	WEU	IRL	Drug product release, release testing labeling and packaging	CTL	08/12 - 15/2011 VAI 06/08 - 12/2009 NAI	Submitted to DO for Inspection 9/25/2013	OC RECOMMENDATION	AC	Based on profile and DO recommendation. Reevaluation in Aug.. 2016
GILEAD SCIENCES, INC.	2082946	LOS	USA	Drug product release: labelling and packaging	TCM	07/31 -0 8/7/2013 NAI 07/26 -0 8/3/2012 NAI	10 day letter submitted to DO 9/25/2013	OC RECOMMENDATION	AC	Based on DO Recommendation for packaging and labeling. Reevaluation in August 2017
(b) (4)				Drug product manufacturing, release testing, labeling and packaging	TCM	(b) (4) VAI VAI NAI	Submitted to DO for Inspection (b) (4)	OC RECOMMENDATION	AC	Based on DO Recommendation. Reevaluation in (b) (4)
GILEAD SCIENCES LIMITED	3006709727	WEU	IRL	Drug product release and release testing, labeling and packaging	TCM	08/12 - 15/2011 VAI 06/08 - 12/2009 NAI	Submitted to DO for Inspection 9/25/2013	OC RECOMMENDATION	AC	Based on last inspection for profile TCM and DO recommendation

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## V. Overall Conclusions and Recommendations

<b>Is the application filable? Yes</b> yes
<b>At this time, is a KTM warranted for any PAI? NO</b>
<b>Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? NO</b>
Comments for 74 Day Letter
1.
2.
3.

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
For Pre-Marking Applications

**REVIEW AND APPROVAL**  
(DARRTS)

APPEARS THIS WAY ON ORIGINAL



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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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VIPULCHANDRA N DHOLAKIA  
03/20/2014

MAHESH R RAMANADHAM  
03/21/2014

# FILING REVIEW and INITIAL QUALITY ASSESSMENT

## FILING REVIEW –NDA 205858

<b>NDA Number:</b>	<b>Supplement Number and Type:</b>	<b>Established/Proper Name:</b>
205858	000	Idelalisib tablets
<b>Applicant:</b>	<b>Letter Date:</b>	<b>Stamp Date:</b>
Gilead Sciences, Inc.	11-Sep-2013	11-Sep-2013

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*				
<b>* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a <i>potential</i> filing issue or a <i>potential</i> review issue.</b>				
	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? <b>This question is not applicable for synthesized API.</b>			N.A.

	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		

	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
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: <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

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

<b>D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
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	

<b>E. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
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.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

<b>F. METHODS VALIDATION (MV)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
29.	Is there a methods validation package?	X		

<b>G. MICROBIOLOGY</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product			N.A.

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

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

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	<b>IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?</b>	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			
36.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?	X		See comments below.

*Filing Letter Comments to the NDA applicant:*

1. We do not agree with the designation of (b) (4) as a regulatory starting material (b) (4) (b) (4) (b) (4) should be designated as the regulatory starting material.

2. Section 3.2.S.2.2 describes (b) (4) and (b) (4) of (b) (4) and Idelalisib. Provide a tabular summary of (b) (4) and Idelalisib batches that were either (b) (4) or (b) (4) and the reason.

Janice Brown, M.S., CMC Lead  
 Division 1, Branch 2  
 Office of New Drug Quality Assessment  
 (See electronic signature stamp)

Ali Al Hakim, Ph.D., Chief Branch 2  
 Division 1, Branch 2  
 Office of New Drug Quality Assessment  
 (See electronic signature stamp)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JANICE T BROWN  
10/07/2013

ALI H AL HAKIM  
10/07/2013