# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 206545Orig1s000

# CHEMISTRY REVIEW(S)

**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 [redacted] It is a white to almost white [redacted] substance. Idelalisib is designated as a BCS class II with low solubility and high permeability. Idelalisib can exist in two [redacted] forms, Form I and Form II. [redacted] is manufactured consistently and used for the manufacture of the drug product. [redacted] Stability data has been provided which demonstrate that there is no [redacted] on storage. Both forms have comparable solubility and other relevant physical properties. Because of no [redacted] and comparable solubility, the risk of product failure based on drug substance polymorphic form is acceptable. The drug substance synthesis is a [redacted] 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 [redacted] months when stored under controlled room temperature.

**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 [redacted] 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, [redacted], 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 15-30ºC (59-86ºF).

**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**

# Table of Contents

# 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 | Document Date |
|---|---|
| Original IND 101254 submission (SD 003) | 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 & 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 p110δ (PI3Kδ)

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

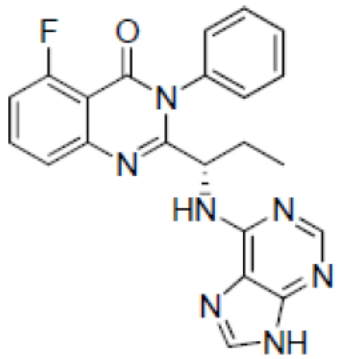
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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: $C_{22}H_{18}FN_7O$
Formula Weight: 415.42

Chemical Structure:




## 17. RELATED/SUPPORTING DOCUMENTS:

### A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | LoA date |
|---|---|---|---|---|---|---|
| (b) (4) | III | (b) (4) | | 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 |

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

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<br>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

# 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 [redacted (b) (4)] It is a white to off-white, [redacted (b) (4)] solid. 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 [redacted (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 [redacted (b) (4)] forms are Form I and Form II. Both forms are similar with respect to solubility and other physical properties. [redacted (b) (4)] is manufactured consistently using the proposed manufacturing method [redacted (b) (4)] [redacted (b) (4)] tability data demonstrated that [redacted (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 [redacted (b) (4)] is low.

Idelalisib is synthesized from a [redacted] (b) (4) The material attributes of the starting materials are controlled by specifications. The reaction intermediates are also [redacted] (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 [redacted] (b) (4)

[redacted] (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 [redacted] (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 [redacted] (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.

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 (b) (4) (b) (4) foil liner.

The manufacturing of Zydelig tablets involve the following steps: (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.

# 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

**ONDQA Initial Quality Assessment (IQA) and Filing Review**
**CMC and Biopharmaceutics**
**NDA 206545, Idelalisib Tablet, Gilead Sciences, Inc.**

# IQA and Filing Review Cover Sheet

1. **NEW DRUG APPLICATION NUMBER:** 206545

2. **DATES AND GOALS:**

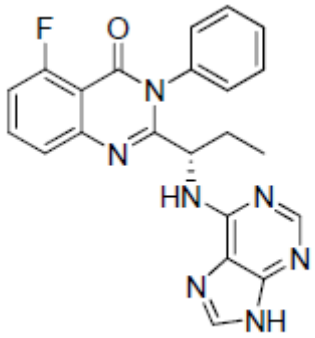
| | |
|---|---|
| Letter Date: 06-Dec-2013 | Submission Received Date: 06-Dec-2013 |
| PDUFA Goal Date: 09-Aug-2014 (Priority) | |

3. **PRODUCT PROPERTIES:**

| | |
|---|---|
| Trade or Proprietary Name: | (b) (4) (Pending) |
| Established or Non-Proprietary Name (USAN): | Idelalisib |
| Dosage Form: | Tablets |
| Route of Administration | Oral |
| Strength/Potency | 150 mg, 100 mg |
| Rx/OTC Dispensed: | Rx |

4. **INDICATION:** Treatment of patients with relapsed chronic lymphocytic leukemia (CLL).

5. **DRUG SUBSTANCE STRUCTURAL FORMULA**:




Empirical Formula: $C_{22}H_{18}FN_7O$
Formula Weight: 415.42

6. **NAME OF APPLICANT**: Gilead Sciences, Inc.

## 7. SUBMISSION PROPERTIES:

| | |
|---|---|
| Review Classification: | Priority |
| Submission Classification (Chemical Classification Code): | Type 1: New molecular entity |
| Application Type: | 505(b)(1) |
| Breakthrough Therapy | No |
| Responsible Organization (Clinical Division): | OHOP/DHP |

## 8. CONSULTS:

| CONSULT | YES | NO | COMMENTS: (list date of request if already sent) |
|---|---|---|---|
| Biometrics | | X | |
| Clinical Pharmacology | | X | |
| Establishment Evaluation Request (EER) | X | | Entered on 20-Dec-2013 |
| Pharmacology/Toxicology | | | Determined by the primary reviewer |
| Methods Validation | X | | Submitted on 04-Oct-2013 for NDA 205858. Both NDAs 205858 and 206545 used the same methods for the DS and DP |
| Environmental Assessment | | X | Categorical exclusion requested per Agency's request |
| CDRH | | X | |
| Other | | X | |

## 9. DMFs

| DMF # | TYPE | HOLDER | ITEM REFERENCED | LOA DATE | COMMENTS |
|---|---|---|---|---|---|
| (b) (4) | Type III | (b) (4) | | 22-Jul-2013 | None |
| | Type III | | | 11-Jun-2013 | None |
| | Type III | | | 24-Jul-2013 | None |
| | Type III | | | 13-May-2013 | None |
| | Type III | | | 19-Jul-2013 | None |
| | Type III | | | 22-Jul-2013 | None |

# Overall Filing Conclusions and Recommendations

## CMC:

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

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

## Biopharmaceutics:

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

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

## Microbiology:

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

**ONDQA Initial Quality Assessment (IQA) and Filing Review**
**CMC and Biopharmaceutics**
**NDA 206545, Idelalisib Tablet, Gilead Sciences, Inc.**

# Summary of Initial Quality Assessment

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

| **Is a team review recommended?** **Yes** | |
|---|---|
| Suggested expertise for team: | |
| **Reviewer** | **Name** |
| CMC | Li Shan Hsieh, Ph.D.(drug product)<br>Debasis Ghosh, Ph.D. (drug substance) |
| Biopharmaceutics | Sandra Suarez, Ph.D. |
| Microbiology | Jessica Cole, Ph.D. |
| CMC Lead | Janice Brown, M.S. |
| Chief, Branch II | Ali Al Hakim, Ph.D. |

# ONDQA Initial Quality Assessment (IQA) and Filing Review
## CMC and Biopharmaceutics
### NDA 206545, Idelalisib Tablet, Gilead Sciences, Inc.

| NDA Number: | Supplement Number and Type: | Established/Proper Name: |
|---|---|---|
| 206545 | 000 | Idelalisib tablets |
| **Applicant:** | **Letter Date:** | **Stamp Date:** |
| Gilead Sciences, Inc. | 06-Dec-2013 | 06-Dec-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 | | Cross referenced NDA 205858 |
| 2. | Is the CMC section indexed and paginated (including all PDF files) adequately? | X | | Cross referenced NDA 205858 |
| 3. | Are all the pages in the CMC section legible? | X | | Cross referenced NDA 205858 |
| 4. | Has all information requested during the IND phase, and at the pre-NDA meetings been included? | | | N.A. |

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

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

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

| C. ENVIRONMENTAL ASSESMENT | | | | |
|---|---|---|---|---|
| | Parameter | Yes | No | Comment |
| 11. | Has an environmental assessment or claim of categorical exclusion been provided? | X | | Requested by the agency |

| D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API) | | | | |
|---|---|---|---|---|
| | Parameter | Yes | No | Comment |
| 12. | Does the section contain a description of the DS manufacturing process? | X | | Cross referenced NDA 205858 |
| 13. | Does the section contain identification and controls of critical steps and intermediates of the DS? | X | | Cross referenced NDA 205858 |
| 14. | Does the section contain information regarding the characterization of the DS? | X | | Cross referenced NDA 205858 |
| 15. | Does the section contain controls for the DS? | X | | Cross referenced NDA 205858 |
| 16. | Has stability data and analysis been provided for the drug substance? | X | | Cross referenced NDA 205858 |
| 17. | Does the application contain Quality by Design (QbD) information regarding the DS? | | X | |
| 18. | Does the application contain Process Analytical Technology (PAT) information regarding the DS? | | X | |

| E. DRUG PRODUCT (DP) | | | | |
|---|---|---|---|---|
| | **Parameter** | **Yes** | **No** | **Comment** |
| 19. | Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging? | X | | Cross referenced NDA 205858 |
| 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 | | Cross referenced NDA 205858 |
| 21. | Is there a batch production record and a proposed master batch record? | X | | Cross referenced NDA 205858 |
| 22. | Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product? | X | | Cross referenced NDA 205858 |
| 23. | Have any biowaivers been requested? | | X | |
| 24. | Does the section contain description of to-be-marketed container/closure system and presentations? | X | | Cross referenced NDA 205858 |
| 25. | Does the section contain controls of the final drug product? | X | | Cross referenced NDA 205858 |
| 26. | Has stability data and analysis been provided to support the requested expiration date? | X | | Cross referenced NDA 205858 |
| 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 | |

| F. METHODS VALIDATION (MV) | | | | |
|---|---|---|---|---|
| | **Parameter** | **Yes** | **No** | **Comment** |
| 29. | Is there a methods validation package? | X | | Cross referenced NDA 205858 |

| G. MICROBIOLOGY | | | | |
|---|---|---|---|---|
| | **Parameter** | **Yes** | **No** | **Comment** |
| 30. | If appropriate, is a separate microbiological section included assuring sterility of the drug product | | | N.A. |

| H. MASTER FILES (DMF/MAF) | | | | |
|---|---|---|---|---|
| | **Parameter** | **Yes** | **No** | **Comment** |

| | | | | |
|---|---|---|---|---|
| 31. | Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete? | X | | Cross referenced NDA 205858 |

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

| K. BIOPHARMACEUTICS | | | | |
|---|---|---|---|---|
| | **Parameter** | **Yes** | **No** | **Comment** |
| 37. | Does the application contain dissolution data? | X | | The following dissolution method is proposed for routine testing:<br>Medium: 750 mL of 0.01 N HCl<br>Apparatus: USP II (paddle)<br>Speed: 75 rpm<br>Temperature: 37˚C (b) (4) |

| | | | | |
|---|---|---|---|---|
| 38. | Is the dissolution test part of the DP specifications? | X | | The proposed acceptance criteria is as follows:<br><br>(b)(4)% at (b)(4) minutes is proposed for both IDELA 100 mg and 150 mg tablets.<br><br>Note: The acceptability of the proposed acceptance criteria is a review issue. |
| 39. | Does the application contain the dissolution method development report including data supporting the discriminating ability? | X | | Yes, there is sufficient information (see sections 3.2.P.2.2; 3.2.P.5.6, and 3.2.P.2.3; document PDM-1442 under section 3.2.p.5.6). The acceptability of this method is a review issue. |
| 40. | Is there a validation package for the analytical method and dissolution methodology? | X | | The amount of idelalisib dissolved is assayed by (b) (4) at (b) (4) and quantified using an external standard. |
| 41. | Does the application include a biowaiver request? | | X | |
| 42. | Is there information/data supporting the biowaiver request? | | X | |
| 43. | Is dissolution testing being proposed as a tool to monitor for crystalline/amorphous content? If so, are data provided to support the discriminating ability of the dissolution method towards different crystalline/amorphous content? | | X | Form I and Form II of idelalisib are indistinguishable by melting point, solubility (0.05 mg/mL) and stability (sections 3.2.p.2.1 and 3.2.S.4.5). (b) (4) |
| 44. | Is there enough information to assess the extended release designation claim? | | X | NA |
| 45. | Is there any information to support the approval of the lower strength (s)? | | | The 150 mg and 100 mg strengths are (b) (4) (Table 1, section 3.2.p.1). There is PK/PD data for both strengths conducted with the tablet formulation (Study 101-02: Phase 1, sequential dose-escalation: study of the safety, PK, PD, and activity of (b) (4) in subjects with relapsed or refractory hematologic malignancies. This study will be reviewed by OCP. |
| 46. | Does the application include an IVIVC model? | | X | |
| 47. | Does the application include information/data on in vitro alcohol dose-dumping potential? | | X | NA |

| | | | | |
|---|---|---|---|---|
| 48. | Is there any in *vivo* BA or BE information in the submission? | X | | There are two BA/BE studies included in the submission:<br>▪ Food effect study: Note that this study was conducted with an early formulation of the product [redacted] (b) (4)) which was shown not to be BE to the clinical formulation (e.g. Cmax upper bound was 1.57).<br>▪ BA/BE study comparing an early formulation [redacted] (b) (4) to the tablet formulation.<br><br>Note: These studies will be reviewed by OCP. |
| 49. | Is there any design space proposed using in vitro release as a response variable? | | X | This submission does not have QbD elements. However, dissolution is being used to support for CMAs and CMPs. |
| 50. | Are there any data supporting a manufacturing change? | | | The commercial product will be manufactured at [redacted] (b) (4). The biobatch was manufactured at [redacted] (b) (4) [redacted] (b) (4) The Applicant will be requested to provide dissolution profile comparisons to bridge these two sites. |
| 51. | Is the control strategy related to in vitro drug release? | | X | Not applicable |

**L. filing conclusion**

| | **Parameter** | **Yes** | **No** | **Comment** |
|---|---|---|---|---|
| 52. | **IS THE PRODUCT BIOPHARMACEUTICS SECTION OF THE APPLICATION FILEABLE?** | X | | • The NDA is fileable from Biopharmaceutics Perspective<br>• The acceptability of the proposed dissolution method and acceptance criterion will be a review issue. |
| 53. | If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant. | | | Not applicable. |
| 54. | If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant. | | | Not applicable. |
| 55. | Are there any potential review issues identified? | | X | |

| | | | | |
|---|---|---|---|---|
| 56. | Are there any comments to be sent to the Applicant as part of the 74-Day letter? | | X | None |
| 57. | Are there any internal comment to other disciplines: | | X | None |

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

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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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