Recommendation: Approval

**NDA 209092**
Review #1

<table>
<thead>
<tr>
<th>Drug Name/Dosage Form</th>
<th>Kisqali® (ribociclib) tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength</td>
<td>200 mg</td>
</tr>
<tr>
<td>Route of Administration</td>
<td>Oral</td>
</tr>
<tr>
<td>Rx/OTC Dispensed</td>
<td>Rx</td>
</tr>
<tr>
<td>Applicant</td>
<td>Novartis Pharmaceuticals Corporation</td>
</tr>
<tr>
<td>US agent, if applicable</td>
<td>N/A</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>SUBMISSION(S) REVIEWED</th>
<th>DOCUMENT DATE</th>
<th>DISCIPLINE(S) AFFECTED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original NDA</td>
<td>8/29/2016</td>
<td>All CMC disciplines</td>
</tr>
<tr>
<td>Quality Amendment (2)</td>
<td>9/9/2016</td>
<td>Drug product</td>
</tr>
<tr>
<td>Quality Amendment (4)</td>
<td>9/19/2016</td>
<td>Drug product/Process</td>
</tr>
<tr>
<td>Quality Amendment (8)</td>
<td>10/5/2016</td>
<td>Drug product/Process</td>
</tr>
<tr>
<td>Quality Amendment (9)</td>
<td>10/17/2016</td>
<td>Drug product/Process</td>
</tr>
<tr>
<td>Quality Amendment (12)</td>
<td>10/26/2016</td>
<td>Drug product/Process</td>
</tr>
<tr>
<td>Labeling/Container-Carton (15)</td>
<td>11/7/2016</td>
<td>Drug product</td>
</tr>
<tr>
<td>Quality Amendment (19)</td>
<td>11/10/2016</td>
<td>Biopharmaceutics</td>
</tr>
<tr>
<td>Quality Amendment (24)</td>
<td>11/23/2016</td>
<td>Drug product/Process</td>
</tr>
<tr>
<td>Quality Amendment (27)</td>
<td>12/14/2016</td>
<td>Drug substance</td>
</tr>
<tr>
<td>Quality Amendment (30)</td>
<td>12/21/2016</td>
<td>Drug product/Process</td>
</tr>
<tr>
<td>Quality Amendment (35)</td>
<td>1/17/2016</td>
<td>Drug substance/ Drug product/Process/Biopharm</td>
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<tr>
<td>Quality Amendment (40)</td>
<td>2/6/2016</td>
<td>Process</td>
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<td>Quality Amendment (43)</td>
<td>2/13/2016</td>
<td>Biopharmaceutics</td>
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<td>Quality Amendment (44)</td>
<td>2/14/2016</td>
<td>Drug substance</td>
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<tr>
<td>Quality Amendment (45)</td>
<td>2/16/2016</td>
<td>Biopharmaceutics</td>
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<tr>
<td>Quality Amendment (49)</td>
<td>2/17/2016</td>
<td>Process</td>
</tr>
<tr>
<td>Quality Amendment (51)</td>
<td>2/24/2016</td>
<td>Biopharmaceutics</td>
</tr>
<tr>
<td>Quality Amendment (52)</td>
<td>2/24/2016</td>
<td>Drug substance</td>
</tr>
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### Quality Review Team

<table>
<thead>
<tr>
<th>DISCIPLINE</th>
<th>REVIEWER</th>
<th>BRANCH/DIVISION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Substance</td>
<td>Raymond Frankewich</td>
<td>CDER/OPQ/ONDP/DNDAP1</td>
</tr>
<tr>
<td>Drug Product</td>
<td>Paresma Patel</td>
<td>CDER/OPQ/ONDP/DNDP1</td>
</tr>
<tr>
<td>Process</td>
<td>Sung Kim</td>
<td>CDER/OPQ/OPF/DPA3</td>
</tr>
<tr>
<td>Microbiology</td>
<td>Julie Nemecek</td>
<td>CDER/OPQ/OPF/DPA3</td>
</tr>
<tr>
<td>Facility</td>
<td>Marion Michaelis</td>
<td>CDER/OPQ/OPF/DIA</td>
</tr>
<tr>
<td>Biopharmaceutics</td>
<td>Gerlie Gieser</td>
<td>CDER/OPQ/ONDP/DB</td>
</tr>
<tr>
<td>Regulatory Business Process Manager</td>
<td>Kristine Leahy</td>
<td>CDER/OPQ/OPRO/DRBPMI</td>
</tr>
<tr>
<td>Application Technical Lead Laboratory</td>
<td>Xiao Hong Chen</td>
<td>CDER/OPQ/ONDP/DNDP1</td>
</tr>
<tr>
<td>OTR</td>
<td>N/A</td>
<td>ORA/OO/OMPTO/DMPT0/MDTP</td>
</tr>
<tr>
<td>ORA Lead</td>
<td>Paul Perdue Jr.</td>
<td>CDER/OPQ/ONDP/DNDP1</td>
</tr>
<tr>
<td>Environmental Analysis (EA)</td>
<td>Raanan Bloom</td>
<td>CDER/OPQ/ONDP/DNDP1</td>
</tr>
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</table>
## Quality Review Data Sheet

### 1. RELATED/SUPPORTING DOCUMENTS

#### A. DMFs:

<table>
<thead>
<tr>
<th>DMF #</th>
<th>Type</th>
<th>Holder</th>
<th>Item Referenced</th>
<th>Status</th>
<th>Date Review Completed</th>
<th>Comments</th>
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<tbody>
<tr>
<td></td>
<td>Type III</td>
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<td>Adequate</td>
<td>2-23-2017</td>
<td>Reviewed by Paresma Patel</td>
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<td>Adequate</td>
<td>2-13-2017</td>
<td>Reviewed by Paresma Patel</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>DOCUMENT</th>
<th>APPLICATION NUMBER</th>
<th>DESCRIPTION</th>
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<tbody>
<tr>
<td>IND</td>
<td></td>
<td>Parent IND</td>
</tr>
<tr>
<td>IND</td>
<td>117796</td>
<td>Breast cancer</td>
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</table>

### 2. CONSULTS

<table>
<thead>
<tr>
<th>DISCIPLINE</th>
<th>STATUS</th>
<th>RECOMMENDATION</th>
<th>DATE</th>
<th>REVIEWER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biostatistics</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacology/Toxicology</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDRH</td>
<td>N/A</td>
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</tr>
<tr>
<td>Clinical</td>
<td>N/A</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>N/A</td>
<td></td>
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</tr>
</tbody>
</table>
Executive Summary

I. Recommendations and Conclusion on Approvability

Sufficient CMC information is provided to support approval of Kisqali® (ribociclib) tablets. There are no outstanding CMC deficiencies for the NDA. The overall recommendation for the facility evaluation is “Acceptable”. Therefore, the NDA is recommended for Approval from the CMC standpoint.

There will be a PMC to perform Post-Marketing Studies to validate the HPLC method for drug quantification, to gather dissolution data at 30 min using HPLC, as well as to refine the approved dissolution acceptance criterion as additional in vivo PK data become available. The following PMC will be conveyed to the applicant and will be finalized when the agreement has been reached between the Agency and the applicant.

“Conduct additional in vitro studies to support the discriminating ability of the dissolution acceptance criterion \( Q = \frac{\text{(% at 45 min)}}{\text{(45 min)}} \) using the approved dissolution method with a validated HPLC analytical method for drug quantification.

Please note, the aim of the Biopharmaceutics PMC is to support the discriminating ability of the dissolution acceptance criterion for routine QC testing of ribociclib tablets at batch release and during stability testing as described below.

i. In vitro dissolution profile data and the corresponding in vivo PK data from batches of the film-coated tablets used in planned post-marketing clinical studies will be provided. The in vitro and the in vivo data generated will be used to validate the current PBPK model.

ii. The current (or a suitable alternative) HPLC analytical method for dissolution testing of ribociclib film-coated tablets will be validated. The analytical method validation will evaluate the robustness of both the dissolution and drug quantification methods (e.g., with respect to type of sampling technique, paddle speed, pH of the dissolution medium, Normality and volume of the dissolution medium, UV wavelength, replacement of media withdrawn during dissolution testing), in addition to precision, specificity, linearity, range, accuracy, solution stability, and filter compatibility.

iii. Batch release testing of intended commercial drug product batches will include comparison of dissolution profiles to the BE batch, using the approved QC dissolution method (by HPLC).

iv. Long-term stability testing on the commercial batches will be conducted for up to 12 months; dissolution data at 30 min and 45 min using the approved QC dissolution method (by HPLC) will be collected.”
II. Summary of Quality Assessments

A. Product Overview
Ribociclib succinate is a synthetically derived new molecular entity. It is a cyclin dependent kinase inhibitor (CDKi), which in combination with letrozole, is indicated for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer as initial endocrine-based therapy. Ribociclib is formulated as an immediate release tablet containing 200 mg active ingredient. During drug development, capsule formulation was used in the clinical trials. A BE study was performed to bridge the capsule formulation and the commercial tablet formulation.

<table>
<thead>
<tr>
<th>Proposed Indication(s) including Intended Patient Population</th>
<th>KISQALI is a kinase inhibitor indicated in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of Treatment</td>
<td>Until disease progression or unacceptable toxicity</td>
</tr>
<tr>
<td>Maximum Daily Dose</td>
<td>KISQALI tablets are taken orally with or without food in combination with letrozole. Recommended starting dose: 600 mg orally (three 200 mg tablets) taken once daily with or without food for 21 consecutive days followed by 7 days off treatment.</td>
</tr>
<tr>
<td>Alternative Methods of Administration</td>
<td>N/A</td>
</tr>
</tbody>
</table>

B. Quality Assessment Overview

Drug Substance
Ribociclib succinate (LEE011) is an orally bioavailable, highly-selective small molecule inhibitor of cyclin-dependent kinase (CDK) 4 / 6. The chemical name is Butanedioic acid—7-Cyclopentyl-N,N-dimethyl-2-{{5-(piperazin-1-yl)pyridin-2-yl}amino}-7H-pyrrolo[2,3-α]pyrimidine-6-carboxamide (1/1). The chemical structure is provided below:

![Chemical Structure](image)

C_{23}H_{30}N_{8}O \cdot C_{4}H_{6}O_{4}
Molecular Weight  552.64
The ribociclib succinate drug substance is a light yellow to yellowish brown crystalline powder. Ribociclib succinate drug substance is slightly hygroscopic. Ribociclib succinate drug substance is classified as a moderately permeable compound. Polymorphism studies showed that ribociclib succinate may exist in different crystalline forms.

Ribociclib succinate has low aqueous solubility.

The manufacturing process of ribociclib succinate is characterized and the physical properties are adequately understood. The manufacturing, controls, packaging and stability characteristics of ribociclib succinate are reasonably understood. The drug substance information is deemed acceptable, and is recommended for approval.

**Drug Product**

The drug product Ribociclib 200 mg film-coated tablet is an immediate release dosage form for oral administration. The proposed starting dose is 600 mg, daily. The applicant has provided an adequate description of the drug product formulation development, excipient compatibility, specifications, analytical methods, and container closure information. The compatibility of the drug product formulation with the proposed container closure systems is supported by stability data. The proposed shelf life of 24 months at 25°C with excursions permitted is supported by registration stability data. The applicant provides adequate post-approval stability protocols and commitments. The drug product ribociclib 200 mg film coated tablets is recommended for approval from the drug product perspective.

**Process**

Manufacturing process consists of three validation batches using new process parameters were manufactured successfully at the intended commercial manufacturing site. Recommend for approval from process perspective.

**Microbiology**
KISQALI (Ribociclib, LEE011); 200 mg is an immediate release solid oral dosage form. There is a minimal risk of microbial proliferation during the manufacturing of the solid oral dosage form. The applicant’s manufacturing process is consistent with regulatory expectations for a non-sterile oral tablet. The specifications for microbial enumeration and the absence of *E. coli* are consistent with those suggested in USP <1111> for an oral tablet.

**Biopharmaceutics**

The Applicant’s proposed QC (quality control) dissolution method and acceptance criterion as provided in the NDA are deemed Adequate. The Applicant’s commitment to perform Post Marketing Studies to validate the HPLC method for drug quantification, to gather dissolution data at 30 min using HPLC, as well as to refine the approved dissolution acceptance criterion as additional *in vivo* PK data become available are Acceptable.

The Applicant did not formally request a BCS designation for the proposed drug product, ribociclib film-coated tablets, but stated that the drug substance can be categorized as BCS Class IV (low solubility/low permeability).

**Facility**

Adequate descriptions were provided for the following facilities; Suzhou Novartis Parma Technology Co Ltd (FEI: 3007114474), Jiangsu, China; Novartis Grimsby Ltd. (FEI: 10656), United Kingdom; Novartis International Pharmaceutical Ltd./ International Services Lab (FEI 3003627233), Cork, Ireland; Novartis Pharma AG (FEI: 3002807772) Basal, Switzerland; Novartis Pharma Schweizerhalle AG (FEI:3002865753), Switzerland; Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd. (FEI: 3006627732), Singapore; Novartis Pharma Produktions GmbH (FEI: 3000978864), Germany; P

There was one pre-approval inspection conducted 2/14-18/2017 at Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd. The initial recommendation from the field for the inspection was NAI. The investigation into OOS for tablet hardness at process validation was acceptable. The EIR was still pending due to the short timeframe from the inspection being conducted and primary review due date. An expedited review for the pre-approval inspection was conducted based on the initial field recommendation and is documented under CMS WA #151870. Approval is recommended for this facility.

At the time of this review all facilities associated with this NDA are in a favorable compliance status for the manufacturing associated with this application. From a facility perspective approval is recommended for all facilities associated with this NDA as documented at the time of this review.

**Environmental Assessment**
The applicant’s claim of categorical is appropriate for the anticipated amount of drug to be used. No “extraordinary circumstances” are indicated. The applicant’s claim of categorical exclusion is acceptable.

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (see Attachment)

OVERALL ASSESSMENT AND SIGNATURES:

Application Technical Lead Name and Date:

This application is recommended for APPROVAL from the CMC perspective.

Xiao Hong Chen, Ph.D.
March 1, 2017
LABELING

R Regional Information

1.14 Labeling

The most recent carton and container labels were submitted on 03-Feb-2017 (SD39) and are copied and reviewed below. The amendment SD39 provides updated NDC numbers. The labels were updated on 20-Dec-2016 (SD29) in response to information requests evaluated below. Samples of the cartons, blister sleeves, and blister cards were submitted to the Agency.

The following IRs were sent to the applicant on 05-Dec-2016 and responses received on 20-Dec-2016 (SD29):

- Provide an Rx only statement on all draft pull out blister cards.
  Applicant Response: An Rx only statement is provided on all draft pull out blister cards.
  Evaluation: Adequate.

- Revise the storage conditions on blister card sleeves and carton labeling to read ‘Store at 20°C to 25°C (68°F to 77°F)’ to be consistent with USP controlled room temperature.
  Applicant Response: The storage conditions have been revised on the blister card sleeves, carton labeling, and draft PI.
  Evaluation: Adequate.

- The NDC number for the 400 mg dose and 600 mg dose blister cards is not visible when the blister card is pulled out. Revise the location of the NDC number so that the number is visible upon pulling the blister card out of the sleeve.
  Applicant Response: The NDC numbers have been relocated to be visible upon pulling the blister cards out of the sleeve.
  Evaluation: Adequate.

- Submit representative samples of tablets in each of the proposed container closure systems for at least one dose.
  Applicant Response: Therefore, the applicant provided representative samples of the proposed container closure system for each dose without tablets. The applicant communicated this information to the Agency prior to shipping the samples.
  Evaluation: The applicant provides adequate samples of the container closure system and implemented the suggestions from DMEPA and CMC. Adequate.
The drug product is available in three presentations:

1) **600 mg daily dose**: A blister pack with 21 tablets per blister pack, and 3 blisters per outer container. A total of 63 tablets per container.

2) **400 mg daily dose**: A blister pack with 14 tablets per pack, and 3 blisters per outer container. A total of 42 tablets per container.

3) **200 mg daily dose**: A blister pack with 21 tablets per blister pack, and 1 blister per outer container. A total of 21 tablets per container.

**Immediate Container Label**

**Blister Cards:**

(b)(4)
Table 1. Blister Cards: Immediate Container Label Review of Regulatory Requirements

<table>
<thead>
<tr>
<th>Item</th>
<th>Comments on the Information Provided in NDA</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))</td>
<td></td>
<td>Adequate</td>
</tr>
<tr>
<td>Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))</td>
<td></td>
<td>Adequate</td>
</tr>
<tr>
<td>Route of administration 21.CFR 201.100(b)(3))</td>
<td>N/A for oral dosage forms</td>
<td></td>
</tr>
<tr>
<td>Net contents* (21 CFR 201.51(a))</td>
<td></td>
<td>Adequate</td>
</tr>
<tr>
<td>Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**</td>
<td>N/A for oral drugs</td>
<td></td>
</tr>
<tr>
<td>Lot number per 21 CFR 201.18</td>
<td></td>
<td>Adequate</td>
</tr>
<tr>
<td>Expiration date per 21 CFR 201.17</td>
<td></td>
<td>Adequate</td>
</tr>
<tr>
<td>“Rx only” statement per 21 CFR 201.100(b)(1)</td>
<td>Addressed by IR, Edits submitted 20-Dec-2016.</td>
<td>Adequate</td>
</tr>
<tr>
<td>Storage (not required)</td>
<td>N/A, not required</td>
<td></td>
</tr>
<tr>
<td>NDC number (per 21 CFR 201.2) requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)</td>
<td>Location of NDC on blister revised to make visible. Refer to IR to applicant above. Edits submitted on 20-Dec-2016. NDC numbers updated 03-Feb-2017.</td>
<td>Adequate</td>
</tr>
<tr>
<td>Bar Code per 21 CFR 201.25(c)(2)**</td>
<td></td>
<td>Adequate</td>
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<tr>
<td>Name of manufacturer/distributor (21 CFR 201.1)</td>
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<td>Adequate</td>
</tr>
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</table>

*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.

**For solid oral dosage forms, CDER policy provides for exclusion of “oral” from the container label

**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.
Blister Sleeves

(b)(4)

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page
## Table 2. Blister Sleeves Immediate Container Label Review of Regulatory Requirements

<table>
<thead>
<tr>
<th>Item</th>
<th>Comments on the Information Provided in NDA</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proprietary name, established name (font size and prominence (FD&amp;C Act 502(e)(1)(A)(i), FD&amp;C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))</td>
<td></td>
<td>Adequate</td>
</tr>
<tr>
<td>Strength (21 CFR 201.10(d)(1); 21 CFR 201.100((d)(2))</td>
<td></td>
<td>Adequate</td>
</tr>
<tr>
<td>Net contents (21 CFR 201.51(a))</td>
<td></td>
<td>Adequate</td>
</tr>
<tr>
<td>Lot number per 21 CFR 201.18</td>
<td></td>
<td>Adequate</td>
</tr>
<tr>
<td>Expiration date per 21 CFR 201.17</td>
<td></td>
<td>Adequate</td>
</tr>
<tr>
<td>Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21 CFR 201.100(d)(2)]</td>
<td></td>
<td>N/A oral drug</td>
</tr>
<tr>
<td>Sterility Information (if applicable)</td>
<td></td>
<td>N/A oral drug</td>
</tr>
<tr>
<td>“Rx only” statement per 21 CFR 201.100(d)(2), FD&amp;C Act 503(b)(4)</td>
<td></td>
<td>Adequate</td>
</tr>
<tr>
<td>Storage Conditions</td>
<td>Revised to be consistent with USP.</td>
<td>Adequate</td>
</tr>
<tr>
<td>NDC number (per 21 CFR 201.2)(requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)</td>
<td>Updated on 03-Feb-2017 (SD39).</td>
<td>Adequate</td>
</tr>
<tr>
<td>Bar Code per 21 CFR 201.25(c)(2)**</td>
<td></td>
<td>Adequate</td>
</tr>
<tr>
<td>Name of manufacturer/distributor</td>
<td></td>
<td>Adequate</td>
</tr>
<tr>
<td>“See package insert for dosage information” (21 CFR 201.55)</td>
<td>The applicant provides dosage information on carton and sleeve.</td>
<td>Adequate</td>
</tr>
<tr>
<td>“Keep out of reach of children” (optional for Rx, required for OTC)</td>
<td></td>
<td>Adequate</td>
</tr>
<tr>
<td>Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))</td>
<td></td>
<td>N/A oral drug</td>
</tr>
</tbody>
</table>
Reviewer’s Assessment: Adequate.

Blister Card
The applicant revised the blister sleeve to include an Rx only statement. Additionally, the location of the NDC number was revised to make the number visible upon pulling out the blister card. The revised blister sleeves were submitted on 20-Dec-2016 (SD29), and NDC numbers were updated on 03-Feb-2017 (SD39).

Blister Sleeve
The applicant revised the blister sleeve during the review cycle based on information requests from the Agency. The storage conditions were revised to ‘Store at 20°C to 25°C (68°F to 77°F)’ and are consistent with USP controlled room temperature. The applicant revised the dosage information from ‘ to providing the recommended dosage information on the blister sleeve. As per 21 CFR 201.55, if the ‘recommended or usual dosage can be set forth on the label, it should appear theron.’ Therefore, the usual dosage is adequate.

The blister cards and blister sleeves meet all the regulatory requirements for immediate container labeling shown above in Table 1 and Table 2. The applicant provided the suggested edits to the labels on 20-Dec-2016, and the revisions are adequate. The NDC numbers were updated by the applicant on 03-Feb-2017, and the updated blister cards, blister sleeves, and carton labeling were submitted as an amendment (SD39).

Carton Labeling

Outer Carton for 600 mg daily dose, 63 tablets:
Outer Carton for 400 mg daily dose 42 tablets:

Outer Carton for 200 mg daily dose, 21 tablets:
<table>
<thead>
<tr>
<th>Item</th>
<th>Comments on the Information Provided in NDA</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proprietary name, established name (font size and prominence (FD&amp;C Act 502(e)(1)(A)(1), FD&amp;C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))</td>
<td></td>
<td>Adequate</td>
</tr>
<tr>
<td>Strength (21 CFR 201.10(d)(1); 21 CFR 201.100(d)(2))</td>
<td></td>
<td>Adequate</td>
</tr>
<tr>
<td>Net contents (21 CFR 201.51(a))</td>
<td></td>
<td>Adequate</td>
</tr>
<tr>
<td>Lot number per 21 CFR 201.18</td>
<td></td>
<td>Adequate</td>
</tr>
<tr>
<td>Expiration date per 21 CFR 201.17</td>
<td></td>
<td>Adequate</td>
</tr>
<tr>
<td>Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables) [201.10(a), 21 CFR 201.100(d)(2)]</td>
<td></td>
<td>N/A oral drug</td>
</tr>
<tr>
<td>Sterility Information (if applicable)</td>
<td></td>
<td>N/A oral drug</td>
</tr>
<tr>
<td>“Rx only” statement per 21 CFR 201.100(d)(2), FD&amp;C Act 503(b)(4)</td>
<td></td>
<td>Adequate</td>
</tr>
<tr>
<td>Storage Conditions</td>
<td>Revised to be consistent with USP.</td>
<td>Adequate</td>
</tr>
<tr>
<td>NDC number (per 21 CFR 201.2) requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)</td>
<td>Updated on 03-Feb-2017 (SD39).</td>
<td>Adequate</td>
</tr>
<tr>
<td>Bar Code per 21 CFR 201.25(c)(2)**</td>
<td></td>
<td>Adequate</td>
</tr>
<tr>
<td>Name of manufacturer/distributor</td>
<td></td>
<td>Adequate</td>
</tr>
<tr>
<td>“See package insert for dosage information” (21 CFR 201.55)</td>
<td></td>
<td>Adequate</td>
</tr>
<tr>
<td>“Keep out of reach of children” (optional for Rx, required for OTC)</td>
<td></td>
<td>Adequate</td>
</tr>
<tr>
<td>Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))</td>
<td></td>
<td>N/A oral drug</td>
</tr>
</tbody>
</table>
Reviewer’s Assessment: Adequate.
The applicant revised the carton labeling during the review cycle based on an information request from the Agency. The storage conditions were revised to ‘Store at 20°C to 25°C (68°F to 77°F)’ and are consistent with USP controlled room temperature. The applicant revised the dosage information from (b)(4) to providing the recommended dosage information on the blister sleeve and carton.

As per 21 CFR 201.55, if the ‘recommended or usual dosage can be set forth on the label, it should appear theron.’ Therefore, the usual dosage information on the carton labels is adequate.

The carton labels meet all the regulatory requirements shown above in Table 3. The applicant provided the suggested edits to the labels on 20-Dec-2016, and the revisions are adequate. The NDC numbers were updated by the applicant on 03-Feb-2017, and the updated blister cards, blister sleeves, and carton labeling were submitted as an amendment (SD39).

**Package Insert**

The package insert was revised in response to information requests from DMEPA and CMC. The suggested modifications to the PI from DMEPA and CMC are shown in the assessment section, and the applicant’s response is evaluated.

**Highlights**

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: 200 mg (3)

**Reviewer’s Assessment:** No edits are suggested, the Highlights section Dosage forms and strengths is adequate.

**Adequate.**

3 **DOSAGE FORMS AND STRENGTHS**

Film-coated tablet: 200 mg ribociclib (equivalent to 254.40 mg ribociclib succinate)

Light greyish violet, (b)(4) round, curved with beveled edges, debossed with “RIC” on one side and “NVR” on the other side.

**Reviewer’s Assessment:** Adequate.
The following suggested edits were sent to the applicant: film coated is moved to the second line for the description of the tablets. The term (b)(4) is removed in the description.

3 **DOSAGE FORMS AND STRENGTHS**

Tablet: 200 mg ribociclib (equivalent to 254.40 mg ribociclib succinate)

Film coated, light greyish violet, round, curved with beveled edges, debossed with “RIC” on one side and “NVR” on the other side.

The applicant made the suggested edits to the Dosage Forms and Strengths section of the PI, and the revised PI was submitted on 21-Feb-2017 (SD50).
11 DESCRIPTION

KISQALI (ribociclib) is a \( (b) \) kinase \( (b) \) inhibitor.

The chemical name of ribociclib is: Butanedioic acid—7-cyclopentyl-\( N,\text{-}N \)-dimethyl-2-\{5-(piperazin-1-yl) pyridin-2-yl\}amino\-7\( H \)-pyrrolo[2,3-\( d \)]pyrimidine-6-carboxamide (1/1).

The molecular formula for ribociclib succinate is \( C_{23}H_{30}N_{8}O \cdot C_4H_6O_4 \) and the molecular weight is 552.64 g/mol (Free base: 434.55 g/mol Salt form).

The chemical structure of ribociclib is shown below:

![Chemical structure of ribociclib](image)

KISQALI film-coated tablets are supplied for oral administration and contain 200 mg of ribociclib free base (equivalent to 254.40 mg ribociclib succinate). The tablets also contain colloidal silicon dioxide, crospovidone, hydroxypropylcellulose, magnesium stearate and microcrystalline cellulose. The film-coating contains iron oxide black, iron oxide red, lecithin (soya), polyvinyl alcohol (partially hydrolysed), talc, titanium dioxide, and xanthan gum as inactive ingredients.

**Reviewer's Assessment:** Adequate.

The following suggested edits were sent to the applicant: the chemical name was revised from ribociclib to ribociclib succinate, and the physical description of the drug substance was added.

11 DESCRIPTION

KISQALI (ribociclib) is a kinase inhibitor.

The chemical name of ribociclib succinate is: Butanedioic acid—7-cyclopentyl-\( N,\text{-}N \)-dimethyl-2-\{5-(piperazin-1-yl) pyridin-2-yl\}amino\-7\( H \)-pyrrolo[2,3-\( d \)]pyrimidine-6-carboxamide (1/1).

Ribociclib succinate is a light yellow to yellowish brown crystalline powder. The molecular formula for ribociclib succinate is \( C_{23}H_{30}N_{8}O \cdot C_4H_6O_4 \) and the molecular weight is 552.64 g/mol (Free base: 434.55 g/mol).

The chemical structure of ribociclib is shown below:
KISQALI film-coated tablets are supplied for oral use and contain 200 mg of ribociclib free base (equivalent to 254.40 mg ribociclib succinate). The tablets also contain colloidal silicon dioxide, crospovidone, hydroxypropylcellulose, magnesium stearate and microcrystalline cellulose. The film-coating contains iron oxide black, iron oxide red, lecithin (soya), polyvinyl alcohol (partially hydrolysed), talc, titanium dioxide, and xanthan gum as inactive ingredients.

The applicant made the suggested edits to the Description Section of the PI, and the revised PI was submitted on 21-Feb-2017 (SD50).

16 HOW SUPPLIED/STORAGE AND HANDLING

KISQALI (ribociclib) Tablets

Light greyish violet, round, curved with beveled edge, debossed with “RIC” on one side and “NVR” on the other side; available in:

Blister pack (21 tablets) – each blister pack contains 21 tablets (200 mg per tablet) (600 mg daily dose)
Outer container - 3 Blister packs per outer container

Blister pack (14 tablets) – each blister pack contains 14 tablets (200 mg per tablet) (400 mg daily dose)
Outer container - 3 Blister packs per outer container

Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Store in the original package.

Reviewer’s Assessment: Adequate.

The following suggested edits were sent to the applicant: the tablet strength was included, the description was removed, the description of the 200 mg daily dose blister pack is included, the storage conditions were updated to be consistent with the USP, and the was removed for the purposes of the PI. The applicant removed the excursions permitted statement to be consistent with the carton/container labeling. The NDC numbers were added and updated to be consistent with amendment SD 39. Additional edits were suggested for the presentation of daily dosage from DMEPA.

16 HOW SUPPLIED/STORAGE AND HANDLING

KISQALI (ribociclib) Tablets

Each film-coated tablet contains 200 mg of ribociclib free base.
Light greyish violet, round, curved with beveled edge, debossed with “RIC” on one side and “NVR” on the other side; available in:

Blister pack (21 tablets) – each blister pack contains 21 tablets (200 mg per tablet) (600 mg daily dose)
Outer container - 3 Blister packs per outer container NDC 0078-0874-63

Blister pack (14 tablets) – each blister pack contains 14 tablets (200 mg per tablet) (400 mg daily dose)
Outer container - 3 Blister packs per outer container NDC 0078-0867-42
Blister pack (21 tablets) – each blister pack contains 21 tablets (200 mg per tablet) (200 mg daily dose)
Outer container – 1 Blister pack per outer container NDC 0078-0860-01

Store at 20°C to 25°C (68°F to 77°F). Store in the original package.

The applicant made the suggested edits to How Supplied/Storage and Handling section of the PI, and the revised PI was submitted on 21-Feb-2017 (SD50).

**Primary Labeling Reviewer Name and Date:**

Paresma Patel, Ph.D.
February 24, 2017

**Secondary Reviewer Name and Date (and Secondary Summary, as needed):**

Anamitro Banerjee, Ph.D.
February 24, 2017
MICROBIOLOGY

Product Background:

NDA: 209092

Drug Product Name / Strength: KISQALI (Ribociclib, LEE011); 200 mg

Route of Administration: Film-coated oral tablet

Applicant Name: Novartis Pharmaceuticals Corporation

Manufacturing Site: Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd, 10 Tuas Bay Lay, Singapore 637461

Method of Sterilization: Non-sterile, not applicable.

Review Summary: Recommended for Approval

List Submissions being reviewed: 8/29/2016, 9/9/2016

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

Supporting/Related Documents: N/A

Remarks Section: N/A

S Drug Substance

The drug substance is not the focus of this review as the drug product is sterilized during drug product manufacture.

P.1 Description of the Composition of the Drug Product
(description-and-composition.pdf, page 3 of 3)

- Description of drug product – Light grayish violet, no score, round tablet, 11.1 mm in diameter, curved with beveled edge, and debossed with “RIC” on one side and “NVR” on the other side.

- Drug production composition –

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount per 200 mg film-coated tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablet Core</td>
<td></td>
</tr>
</tbody>
</table>
**Description of container-closure system** –

- blister packs consisting of a film backed with a heat sealable lacquered aluminum foil. The film is in contact with the drug product.
- aluminum blister

**Reviewer’s Assessment:** The applicant provided an adequate description of the drug product composition and the container-closure system.

**P.2.5 Microbiological Attributes**

**Container/Closure and Package Integrity** – N/A

**Antimicrobial Effectiveness Testing** – N/A

**Reviewer’s Assessment:** Not applicable, container closure integrity and antimicrobial effectiveness testing is not required for a non-sterile product.

**P.3 Manufacture**

**P.3.1 Manufacturers**

(manufacturers.pdf, page 3 of 3)

Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd.
10 Tuas Bay Lane
Singapore, 637461
(Manufacturing and analytical testing of the drug product)

(Stability testing)
P. 3.3 Description of the Manufacturing Process and Process Controls

(qualit-assessment-manuf-process-and-controls.pdf)

- Overall manufacturing operation
Reviewer’s Assessment: There is a minimal risk of microbial proliferation during the manufacturing of the solid oral dosage form. The applicant’s manufacturing process is consistent with regulatory expectations for a non-sterile oral tablet.

P.5 Control of Drug Product

P. 5.1 Specification

(justification-of-specifications.pdf)

- Endotoxin — N/A
- Sterility — N/A
- The applicant states that microbial enumeration will not be performed. The following microbial enumeration results were provided for production scale batches:

Acceptance criteria
- Total aerobic microbial count (TAMC): <100 CFU/g
- Total yeast and mold count (TYMC): <50 CFU/g
- Specified microorganisms: *E. coli* is absent in 1 g

<table>
<thead>
<tr>
<th>Batch</th>
<th>Manufacturing Step</th>
<th>TAMC</th>
<th>TYMC</th>
<th>Presence of <em>E. coli</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>SD0001/860316</td>
<td>Film-coated tablets</td>
<td>&lt;100 CFU/g</td>
<td>&lt;50 CFU/g</td>
<td>Absent in 1 g</td>
</tr>
<tr>
<td>SD0002/860316</td>
<td>Film-coated tablets</td>
<td>&lt;100 CFU/g</td>
<td>&lt;50 CFU/g</td>
<td>Absent in 1 g</td>
</tr>
<tr>
<td>SD0002/859819</td>
<td>Film-coated tablets</td>
<td>&lt;100 CFU/g</td>
<td>&lt;50 CFU/g</td>
<td>Absent in 1 g</td>
</tr>
<tr>
<td>SD0001/860139</td>
<td>Film-coated tablets</td>
<td>&lt;100 CFU/g</td>
<td>&lt;50 CFU/g</td>
<td>Absent in 1 g</td>
</tr>
<tr>
<td>SD0001/860506</td>
<td>Film-coated tablets</td>
<td>&lt;100 CFU/g</td>
<td>&lt;50 CFU/g</td>
<td>Absent in 1 g</td>
</tr>
</tbody>
</table>
QUALITY ASSESSMENT

There is minimal risk of microbial proliferation in these products. Based on and the provided results, the applicant will not perform microbial enumeration as part of the release testing. Microbial enumeration will instead be performed on the three initial stability batches as follows:

<table>
<thead>
<tr>
<th>Storage condition</th>
<th>6 months</th>
<th>12 months</th>
<th>18 months</th>
<th>36 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accelerated: 40 °C/75% RH</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long term: 25 °C/60% RH</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

The applicant provided results from testing performed on the stability batches after six months stored at 40 °C/75% RH. The three stability batches (1010006019, 101000657, and 1010007209) had a TAMC of less than 100 CFU/g, a TYMC of less than 50 CFU/g, and *E. coli* was not detected in 1 g.

- Microbial enumeration testing is performed for the excipients used in manufacturing the . The following acceptance criteria apply:
  - TAMC: Not more than CFU/g
  - TAYC: Not more than CFU/g
  - Specified micro-organisms: Absence of *E. coli*, *P. aeruginosa*, *S. aureus*, and *Salmonella* spp. in 1 g.

**Reviewer’s Assessment:** The specifications for microbial enumeration and the absence of *E. coli* are consistent with those suggested in USP <1111> for an oral tablet.

**P.5.2 Analytical Procedures**

See Section 5.1.

**P.5.3 Validation of Analytical Procedures:**

Not applicable.

**P.7 Container Closure**

See Section P.1.
P.8 Stability

P.8.1 Stability Summary and Conclusion

Expiry: 24 months

See section 5.1 in regard to the long term and accelerated stability testing.

Reviewer’s Assessment: The applicant has met the regulatory expectations regarding the stability program associated with the subject drug product.

P.8.2 Post-Approval Stability Protocol and Stability Commitment

The applicant commits to placing the first three commercial lots of the subject drug product into their stability program. Thereafter, on an annual basis, one production lot will be added to the stability program.

Reviewer’s Assessment: The applicant has met the regulatory expectations regarding the post-approval stability protocol.

P.8.3 Stability Data

See Section 5.1.

A Appendices

A.2 Adventitious Agents Safety Evaluation
(excipients-human-animal.pdf)

The applicant states that no excipients of human or animal origin are used in the manufacturing of the drug product. The magnesium stearate is of vegetable origin.

A.2.1 Materials of Biological Origin

Reviewer’s Assessment: Not applicable.

A.2.2 Testing at Appropriate Stages of Production

Reviewer’s Assessment: Not applicable.

A.2.3. Viral Testing of Unprocessed Bulk

Reviewer’s Assessment: Not applicable.

A. 2.4 Viral Clearance Studies
Reviewer’s Assessment: Not applicable.

**R  Regional Information**

*Executed Batch Records*

An executed batch record was provided for batch SD0002/860316.

**Reviewer’s Assessment:** The applicant has met the regulatory expectations regarding the executed batch records.

*Comparability Protocols*

No CP was included in the application.

2. **REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1**

2.A. **Package Insert**

Store at 25 °C in the original packaging. Excursions are permitted between 15-30 °C.

**Reviewer’s Assessment:** The applicant has met regulatory expectations with regard to the information related to issues of product quality microbiology that is provided in the product labeling.

**Post-Approval Commitments:** N/A

**Lifecycle Management Considerations:** N/A

**List of Deficiencies:** N/A

**Primary Microbiology Reviewer Name and Date:** Julie Nemecek, 11/21/2016

**Secondary Reviewer Name and Date (and Secondary Summary, as needed):** Dupeh Palmer, 12/5/2016, "I concur".
BIOPHARMACEUTICS

Product Background:

NDA: 209092-ORIG-1
Drug Product Name / Strength: KISQALI® (Ribociclib; LEE011) Immediate-release film-coated tablet, 200 mg (as free anhydrous base; equivalent to 254.4 mg anhydrous succinate salt)
Route of Administration: Oral
Applicant Name: Novartis Pharmaceuticals Corporation

Review Summary:
• The Applicant’s proposed QC dissolution method and acceptance criterion as summarized in the table below are deemed Adequate. The Applicant’s commitment to perform Post-Marketing Studies to validate the HPLC method for drug quantification, to gather dissolution data at 30 min using HPLC, as well as to refine the approved dissolution acceptance criterion as additional in vivo PK data become available are Acceptable.

<table>
<thead>
<tr>
<th>USP Apparatus</th>
<th>Speed</th>
<th>Medium</th>
<th>Volume</th>
<th>Acceptance criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (paddles)</td>
<td>50 rpm</td>
<td>0.01N HCl, pH 2 (degassed) (37 ± 0.5°C)</td>
<td>900 mL</td>
<td>Q = 85% at 45 min</td>
</tr>
</tbody>
</table>

Review Recommendation:
The Division of Biopharmaceutics recommends APPROVAL of NDA 209092 for ribociclib film-coated tablets, 200 mg.

List of Submissions reviewed:
SDN-1, 8/29/2016 (Original)
SDN-2, 9/9/2016 (Sponsor’s Response to Quality Information Request)
SDN-8, 10/05/2016 (Sponsor’s Response to Quality Information Request)
SDN-19, 11/10/2016 (analysis datasets)
SDN-30, 12/21/2016 (Sponsor’s Response to Quality Information Request)
SDN-35, 1/17/2017 (analysis dataset)
SDN-43, 2/13/2017 (Sponsor’s Response to Quality Information Request)
SDN-45, 2/16/2017 (Sponsor’s Response to Quality Information Request)
SDN-51, 2/24/2017 (Sponsor’s Response to Quality Information Request)

Highlight of Key Outstanding Issues from Last Cycle:
Not Applicable

Concise Description of Outstanding Issues:
- Fulfilment of a Post Marketing Commitment, PMC.
**BCS Designation**

**PRIMARY REVIEWER’S Assessment: NOT APPLICABLE**

The Applicant did not formally request a BCS designation for the proposed drug product, ribociclib film-coated tablets, but stated that the drug substance can be categorized as BCS Class IV (low solubility/low permeability).

**Solubility:** Per BCS criteria, ribociclib succinate is considered a low solubility drug substance (0.8 mg/mL of the salt = 0.63 mg/mL of the free base) since at least 158 mg of the free base dissolves in 250 mL of pH 1, 2, 4.5, or 6.8 buffer at 37 °C; higher amounts of ribociclib dissolve at pH <5.5 than at higher pH (see Table 3-3 in Section 3.2.S.3 of the NDA). Note that the reported solubility of the drug substance at 37 °C depends not only on the pH of the medium but also the concentration of drug. Note also that the proposed commercial strength of ribociclib film-coated tablets is 200 mg (as free base) but the proposed starting dosage for use with letrozole in the treatment of breast cancer is 600 mg (3 x 200 mg) once daily (with or without food); if indicated, dosage may be reduced to 200 or 400 mg once daily. [Recently, the Applicant agreed to conduct Clinical Pharmacology-related PMR#1 to compare the efficacy and safety of 600 mg QD to an alternative dosage (300 mg BID or 400 mg QD).]

**Permeability:** Per the Applicant, the drug substance exhibits moderate permeability. In a human radiolabelled ADME Study, 17.3% of the administered dose (3 x 200 mg capsules) was excreted as unchanged ribociclib in the feces.

**Dissolution:** The dissolution of the proposed drug product (200 mg film-coated tablet) is not rapid across the entire physiologic pH range. The drug dissolution of the BE batch (# 1010006019) of ribociclib film-coated tablets was at least % at 30 min in the proposed QC dissolution medium (pH 2.0) as well as in pH 1.0 buffer medium but was lower than % in pH 4.5 and pH 6.8 media; see Figure 3-7 of Section 3.2.P.2, pharmaceutical-development.pdf).

**Dissolution Method and Acceptance Criteria**

**PRIMARY REVIEWER’S Assessment:**

**Dissolution Method – ACCEPTABLE (with Post-Marketing Commitment Studies)**

The proposed dissolution method [USP Apparatus 2 (paddle) at 50 rpm; 900 mL of 0.01N HCl (pH 2, degassed); 37 ± 0.5°C; ]

Per the Applicant, USP Apparatus 2 (paddle) was chosen based on the final dosage form type (tablet) and better ability to show via comparative dissolution profiles the differences in characteristics of drug product batches. A paddle speed of 50 rpm was selected because it was considered a standard paddle speed to ensure complete dissolution without sacrificing discriminating power.
**Drug substance particle size distribution** (DS PSD) may be a critical quality attribute since the API is a low solubility drug substance, per BCS criteria. This Reviewer concludes that the proposed QC dissolution method is sensitive to changes in the particle size distribution of the drug substance used to manufacture the film-coated tablets based on the following observations:
(2) The proposed QC dissolution method was also shown to be sensitive to changes in tablet crushing strength. Figure 2 shows that a decrease in *tablet crushing strength (hardness)* due to moisture uptake during high humidity storage was associated with significant increases in the dissolution rate of one of the primary registration stability batches of the 200 mg ribociclib film-coated tablets.
Figure 2.
Dissolution profiles of a primary registration/stability batch (1010006547) of Ribociclib 200 mg film-coated tablet as a function of packaging and storage conditions, and associated changes in tablet hardness and moisture content.

(3) Like drug substance particle size distribution and tablet hardness, the Applicant considers the film-coating of the tablet to be a critical quality attribute (CQA) affecting dissolution. In the 2/21/2017 teleconference meeting held between the FDA and the Applicant, the production-scale batch (SD0001/860316, from Figure 1 above) manufactured with smaller drug substance particles and higher tablet hardness (as compared to the BE batch) was further altered by applying additional coating. The Applicant reported that the double-coated variant of the already aberrant batch showed an even slower dissolution rate, and did not conform with the Applicant’s proposed QC dissolution acceptance criterion.
QUALITY ASSESSMENT

Since the reported solubility of ribociclib succinate in the proposed QC medium (0.01N HCl, pH 2) is $\geq 8.33 \, \text{mg/mL}$ at 37 °C, sink conditions are anticipated to be achieved and maintained during routine dissolution testing. Note that the pH of the medium equilibrates to the intrinsic pH (~5 to 5.5, depending on the drug concentration) of ribociclib during solubility testing.

The proposed analytical method was validated for specificity, accuracy, linearity, precision, solution stability (5 to 6 days at ambient or refrigerated condition, filter compatibility, and robustness (with respect to sampling type). Based on the Applicant’s 2/13/2017 Response to the FDA Information Request dated 2/7/2017 (regarding mainly the apparent inconsistency in the dissolution profile data of 2 of the 3 primary stability batches of the 200 mg film-coated tablet), it was revealed/clarified that (1) dissolution data presented in the NDA for the tablet were generated using either the proposed UV method or the current HPLC method with UV detection (272 nm) but such distinction was not clarified in the data tables and figures, (2) when considering the dissolution profile data provided for the primary registration (stability) batches other than the BE batch, dissolution data at the 30-min timepoint has a numerically lower mean and is more highly variable when using the proposed method than when using the current HPLC method, (3) the HPLC method was used for dissolution testing of the Phase 3 clinical trial material (200 mg capsule) and was previously successfully validated for precision, specificity, linearity, range, accuracy, solution stability, filter compatibility, i.e., using the capsule rather than the 200 mg film-coated tablet. Based on the Applicant’s response to the information request, this Reviewer recommends the use of the current HPLC method for dissolution testing or the proposed HPLC method for Assay. If the
analytical validation of the HPLC method for dissolution testing using the tablet cannot be performed during the review cycle, a post-marketing study can be considered.

**Dissolution Acceptance Criterion**

The proposed dissolution acceptance criterion is ‘Not less than \( Q \) % in 45 minutes’ of the declared content according to acceptance table 1 of harmonized Ph. Eur., USP and JP (Release: stages 1 and 2 only; Stability: Stages 1, 2, and 3). The setting of Q-value and Q-time was based on the cumulative data available to date for all 200 mg ribociclib film-coated tablet batches manufactured at pilot and commercial scales by the current and the proposed commercial manufacturing sites.

For routine QC dissolution testing of the proposed 200 mg ribociclib film-coated tablets at batch release and during shelf-life, this Reviewer recommends a dissolution acceptance criterion of ‘\( Q = \) % at 30 min’ (using HPLC/UV at 272 nm). The following factors and observations support the Reviewer’s recommendation to tighten the dissolution acceptance criterion of the proposed drug product, as well as to switch the drug quantification method from (proposed) to HPLC/UV at 272 nm (recommended):

1. Per BCS criteria, ribociclib succinate is a low solubility (and low permeability) drug substance, and the proposed 200 mg ribociclib film-coated tablet is not rapidly dissolving drug product across the entire physiologic pH range. Thus, dissolution is a critical test to ensure consistent batch-to-batch performance, as well as bioavailability (since only dissolved drug can permeate passively across cellular membranes en route to systemic absorption).

2. The BE batch (#1010006019) of the film coated tablet (FCT-1) [which was shown to have comparable PK profile to the pivotal Phase 3 clinical drug product (200 mg capsule)] achieves 89% mean dissolution at 30 min (n=12, using HPLC/UV at 272 nm) at Month 19 of long-term (25°C/60%RH) storage; see Reviewer Table 1.

3. This Reviewer’s recommended dissolution acceptance criterion (\( Q = \) % at 30 min) accommodates the two other primary registration/stability batches with similar quality attributes (e.g., DS PSD, process type and scale) and in vitro dissolution profiles as the BE batch (as shown in Figures 3-8 and 3-19 of the PDR; using HPLC/UV at 272 nm for drug quantification), as well as the first successful Process Validation Batch #SD0002/860591 (manufactured at commercial scale via the same process flow using a DS with slightly higher d\(_{50}\) and d\(_{90}\) as and with f\(_2\) >50 relative to the BE batch; see also Reviewer Table 1.

4. For a low solubility drug substance, particle size distribution (PSD) has the potential to influence drug product performance. The dissolution profile data in Figure 1 above shows that 30 min is an appropriate time point for a specification value of \( Q = \) %, if it is desirable to have tablet batches with DS PSD (and tablet hardness) that are comparable to that of the BE batch. Note that the Applicant concluded that the dissolution data generated by HPLC/UV at 272 is comparable (if not numerically higher) than the value generated by...
(5) On the other hand, the 30-min specification time point for a Q of 98% allows for the exclusion of commercial-scale batches similar to Production Batch # SD0001/860316 which failed to demonstrate profile similarity (by f2 analysis) to the BE batch even though its reported mean cumulative dissolution at 45 min was 98% (by HPLC/UV 272 nm) or 92%.

(6) Likewise, the recommended dissolution acceptance criterion (Q = 98% at 30 min; using HPLC/UV at 272 nm) will not allow batches like “failed” Process Validation Batch # SD0001/860591 to pass routine QC dissolution testing; see Table 1 below.

(7) Table 1 also shows that the three “successful” Process Validation batches would conform to the Reviewer’s recommended acceptance criterion at Stage 2 testing (Q = 98% in 30 min, using HPLC/UV at 272 nm for drug quantification.)

(8) Except for the BE batch (#1010006019), there are no clinical trial or PK study batches of the ribociclib 200 mg film-coated tablet with in vitro dissolution profile data that can be considered to justify “loosening” of the Reviewer’s recommended acceptance criterion for routine QC dissolution testing.

Based on the foregoing considerations, this Reviewer believes that a specification time point of 30 min for a Q of 98% is adequate for ensuring batch-to-batch uniformity and bioavailability of the proposed drug product. This Reviewer does not object to the Applicant’s proposal to limit the dissolution testing to USP Stages 1 and 2 only at the time of batch release of the finished drug product.

Table 1. Mean (%RSD) Dissolution at 30 min of Clinical/Primary Registration (Stability), and Process Validation Batches\(^a\) (generated using the current HPLC method with UV detection at 272 nm)

<table>
<thead>
<tr>
<th>Storage Conditions</th>
<th>Months</th>
<th>Batch/Material Number (Batch Type)</th>
<th>N</th>
<th>Mean</th>
<th>CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>25°C/60% RH</td>
<td>19</td>
<td>1010006019/859571(Clinical BE, pilot)</td>
<td>12</td>
<td>89</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>~15</td>
<td>1010006547/859572(Primary Registration/Stability, pilot)</td>
<td>12</td>
<td>91</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>~12</td>
<td>1010007028/859824(Primary Registration/Stability, pilot)</td>
<td>12</td>
<td>88</td>
<td>9</td>
</tr>
<tr>
<td>Initial</td>
<td>0</td>
<td>SD0001/860591(“Failed” Process Validation, production)</td>
<td>12</td>
<td>73(^b)</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD0002/860591(“Successful” Process Validation, production)</td>
<td>12</td>
<td>84</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD0003/860591(“Successful Process Validation, production)</td>
<td>12</td>
<td>88</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD0004/860591(“Successful” Process Validation, production)</td>
<td>12</td>
<td>81</td>
<td>15</td>
</tr>
</tbody>
</table>

\(^a\) Based on Reviewer’s analysis of SAS dataset for dissolution data generated using HPLC/UV (272 nm) for drug quantification at the current stability time point, as well as Sponsor’s Response to Quality Information Request (submitted under SDN-45 and SDN-46).

\(^b\) At 45 min, 98% mean and 3.6% RSD
Bridging of Formulations

PRIMARY Reviewer’s Assessment: ADEQUATE

Note that the pivotal Phase 3 clinical trial material (DiC) is a hard gelatin capsule containing 200 mg drug (free base equivalent) with no excipients, manufactured at pilot scale by Novartis Pharma AG (Basel, Switzerland). In a single-dose Fasted BE study, the PK of the 200 mg DiC was compared to that of a 200 mg ribociclib film-coated tablet (FCT-1; Batch 1010006019) described as dark brown, round, curved with beveled edge, with no score, imprinted (debossed?) with “984” on one side and “NVR” on the other side. Note that the lot of the FCT-1 tablet tested in this BE Study is one of three primary registration/stability pilot-scale batches produced by Novartis (Basel).

The to-be-marketed drug product is a film-coated tablet containing 200 mg drug (FCT-2) described as light greish violet, round, curved with beveled edge, with no score, debossed “RIC” on one side and “NVR” on the other side, approximately 11.1 mm in diameter. The proposed commercial manufacturing site for the to-be-marketed drug product is Novartis (Singapore); the process involves use of pharmaceutical grade excipients and film-coating. Figure 3 shows the in vitro dissolution profiles (in various pH media including the proposed QC dissolution medium) of the BE lot (FCT-1) vs the first of three successful production-scale validation batches (FCT-2) produced in the proposed commercial site using the same formulation (composition) for the tablet core, and the same manufacturing process steps (as used for the batch tested in the BE study) except for minor adjustments in some process parameters. Overall, this process parameter optimization resulted in better matching of the dissolution profile of the BE batch (as shown in Figure 3 below for the first “successful” validation batch, SD002/860591). Based on the dissolution profile data (generated using HPLC) submitted by the Applicant in response to the Biopharmaceutics information request, the next two “successful” Process Validation batches (SD003/860591 and SD004/860591) also exhibited similar dissolution profiles to the BE batch in the QC dissolution medium with profile similarity (f2) values >63 relative to the BE batch at Month 18 of long-term and intermediate stability testing. Note that like the aged BE batch, all three “successful” Process Validation batches at the initial stability time point conformed to this Reviewer’s recommended dissolution acceptance criterion (Q = [###]% at 30 min) by Stage 2 testing, unlike the “failed” Process Validation Batch which used a different manufacturing process flow.
Figure 3. Comparative in vitro dissolution profiles* in various pH media of the BE batch versus the first “successful” commercial-scale validation batch

*The dissolution profiles were generated using USP Apparatus 2 (paddle) at 50 rpm and 900 mL of dissolution media. Regardless of media pH, the calculated profile ($f_2$) similarity values were >50, suggesting similarity of the BE batch to the proposed commercial batch. Based on the Applicant’s response to the Biopharmaceutics Information Request #1, the dissolution profile data depicted in the figure above were generated using the current HPLC method. See SDN-45 for the comparative dissolution profile data generated using the proposed UV method.

Of note, the drug substance (API) lots of DiC, FCT-1 and FCT-2 were all manufactured by Novartis Pharma AG (Basel).

Altogether, the in vivo BE data and the in vitro comparative dissolution profile data provided are adequate to bridge the final (commercial scale) to-be-marketed drug product (FCT-2) to the drug product (DiC) evaluated in the pivotal Phase 3 clinical trial, based on the following lines of evidence:

(1) Per the Clinical Pharmacology Review Team, the test and the reference drug products (i.e., FCT-1 and DiC) are comparable in terms of ribociclib $C_{\text{max}}$, $AUC_{\text{last}}$ and $AUC_{\text{inf}}$.

(2) The in vitro dissolution profile of FCT-2 is similar to that of FCT-1, as shown in Figure 3; the calculated profile similarity values were all >50, regardless of media pH.

(3) The proposed drug product is an immediate-release oral tablet. Thus, in vitro comparative dissolution profile data in QC dissolution media plus in other media with pH across the physiologic range are deemed sufficient to support the FCT-1 to FCT-2 [pre-marketing] change
in the drug product manufacturing site that occurred post-pivotal Phase 3 clinical trial, as well as the change in tablet appearance (dark brown vs light grey and imprint vs debossing), the batch scale-up, and the minor changes in the process parameters, without a change in the tablet formulation and (final) process type and steps.

Post-Approval Commitments

PRIMARY Reviewer’s Assessment:

This Reviewer recommends that the current HPLC method for dissolution testing or a suitable alternative HPLC method (e.g., as proposed for Assay) be adopted. Since analytical validation of the current HPLC method was done using the Phase 3 clinical trial material (i.e., 200 mg ribociclib capsules), supplementary or full analytical method validation should be performed using the proposed commercial drug product (i.e., 200 mg ribociclib film-coated tablets).

In the Applicant’s Response to the FDA post-teleconference comment received on 2/24/2017, the Applicant agreed “to perform dissolution profile testing at pH 2.0 at release with quantitation by HPLC on all batches intended for commercial use, and to demonstrate similarity by multivariate analysis to the BE batch until additional PK data is available, while maintaining the dissolution acceptance criterion of ‘Q = \frac{\text{b}}{\text{a}} \% at 45 min’ for release and stability”. Additionally, the Applicant committed “to provide additional PK data on film-coated tablet batches from clinical trials, and validate the HPLC method of quantitation. As more data become available, Novartis will evaluate the totality of evidence and may submit a supplemental NDA to refine the approved in vitro dissolution acceptance criterion in the future.”

In consideration of the “Priority” status as well as the Breakthrough Therapy designation of this NDA, and the lack of robust dissolution on stability data at the Reviewer’s recommended specification time point to adequately support the CMC Reviewer’s recommendation for expiration dating, this Primary Biopharmaceutics Reviewer defers to the Secondary Reviewer regarding the final decision to accept the proposed dissolution acceptance criterion, and to conduct the appropriate additional Post-Marketing Study related to the refinement of the proposed dissolution acceptance criterion. See the section below for the Post-Marketing Studies recommended to support the approval of this NDA.

List of Deficiencies:

None

Primary Biopharmaceutics Reviewer Name and Date: Gerlie Gieser, PhD (2/24/2017)
OVERALL SECONDARY REVIEWER ASSESSMENT:

I concur with Dr. Gieser's assessment and acceptance recommendation for the proposed dissolution method, including the use of HPLC-UV for quantitation of ribociclib in dissolution samples. Regarding the dissolution acceptance criterion, however, I recommend acceptance of the Applicant’s proposed acceptance criterion ($Q = \% at 45\,\text{min}$) on an interim basis pending fulfilment of the PMC to be finalized prior to the NDA Action date.

The Division of Biopharmaceutics recommends APPROVAL of NDA 209092 for ribociclib film-coated tablets, 200 mg.

The Applicant has made the following commitments in their 2/24/2017 response to FDA’s IR comments:

i. PK data from clinical trials using film-coated batches with the corresponding in vitro dissolution profiles will be provided. The data will be used to validate the PBPK model and will be numerically compared to historical PK data for ribociclib. The target date for submission of the PBPK model is June 30, 2018.

ii. Collection of dissolution data at the FDA recommended specification time point of 30\,\text{min} and to adopt and validate the HPLC method of quantitation. Target submission date: September 30, 2017.

iii. Performance of dissolution profile testing at pH 2.0 at release with quantitation by HPLC on all batches intended for commercial use, and demonstrate similarity to the BE batch by multivariate analysis until additional PK data are available. Target submission date: TBD in the PMC.

In addition to the above, the following will be added to the PMC:

iv. Conduct long-term dissolution stability testing on three primary commercial/registration (stability) batches for up to 24 months. Submit dissolution data at 30\,\text{min} and 45\,\text{min} generated using the approved QC dissolution method with a validated HPLC analytical method for drug quantification.

[Suggested Completion Date of Study Report: 15 months post-approval of NDA]

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Okpo Eradiri, PhD (2/24/2017)
QUALITY ASSESSMENT

ENVIRONMENTAL ANALYSIS

R  Regional Information

Environmental Analysis

NDA 209092: Review of Claim of Categorical Exclusion

The following information is provided in the application:

Novartis Pharmaceuticals Corporation has submitted a claim of categorical exclusion for ribociclib succinate, citing 21CFR25.31(b). A statement of "no extraordinary circumstances" is provided.

The sponsor provides a production value estimate of kg/year for 2021 based on the highest annual quantity of the active moiety expected to be produced for use during the first 5 years of production. The EIC from patient use is calculated as (ppb). This is a worst-case estimate assuming all sold product is discharged as the parent compound through waste water treatment systems.

Ribociclib succinate is indicated in combination with letrozole for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer as initial endocrine-based therapy. Ribociclib is orally bioavailable, highly selective inhibitor of cyclin dependent kinase (CDK)4 and 6 that induces G1 arrest at sub-micromolar concentrations in a variety of pRb-positive cancer cells in vitro.

In vitro and in vivo studies indicate ribociclib undergoes extensive hepatic metabolism in humans mainly via CYP3A4. Ribociclib is extensively metabolized with unchanged drug accounting for 17% in feces and 12% in urine. N-demethylated ribociclib was a significant metabolite in excreta and represented approximately 14% in feces and 4% in urine of the administered dose. Numerous other metabolites were detected in both feces and urine in minor amounts (≤ 3% of the administered dose).

No other information is submitted in support of the claim of categorical exclusion.

Review: Estrogenic, androgenic or thyroid pathway activity is not indicated. Fertility studies in animals have not been performed. According to the drug substance review, ribociclib succinate is considered to have low solubility and is unstable in acidic and basic, as well as hydrolytic and oxidative conditions. These characteristics may limit aquatic exposures. A special issue related to effects of anticancer drug residues in the environment (Environ Sci Pollut Res (2016) 23:14791-14804) shows low likelihood of risk to fish (NOEC) at concentrations below 0.1 ug/L. A search of ecotoxicology literature did not locate any information on the ecological hazards or risks of ribociclib or kinase inhibitors including on the development and reproduction of aquatic organisms. No information was located indicating that at the expected level of exposure, there is the potential for serious harm to the environment.
**Reviewer’s Assessment:** Adequate. The cited claim of categorical is appropriate for the anticipated amount of drug to be used. No “extraordinary circumstances” are indicated. The applicant’s claim of categorical exclusion is acceptable.

**Primary EA Reviewer Name and Date:** Raanan A. Bloom, Ph.D. 2-13-17

**Secondary Reviewer Name and Date (and Secondary Summary, as needed):**
<table>
<thead>
<tr>
<th>Attribute/CQA</th>
<th>Factors that can impact the CQA</th>
<th>Initial Risk Ranking*</th>
<th>Risk Mitigation Approach</th>
<th>Final Risk Evaluation</th>
<th>Lifecycle Considerations/Comments**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay, Stability</td>
<td>· Formulation · Container closure · Raw materials · Process parameters · Scale/equipments · Site</td>
<td>L</td>
<td>Controlled for in specifications.</td>
<td>L</td>
<td>None</td>
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<tr>
<td>Physical stability (solid state)</td>
<td>· Formulation · Raw materials · Process parameters · Scale/equipments · Site</td>
<td>M</td>
<td>Physical form is controlled with DS specifications. The applicant demonstrated that DP polymorphic form does not change on shelf life through IRs.</td>
<td>L</td>
<td>None</td>
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<tr>
<td>Content uniformity</td>
<td>· Formulation · Raw materials · Process parameters · Scale/equipments · Site</td>
<td>L</td>
<td>Controlled for in specifications.</td>
<td>L</td>
<td>None</td>
</tr>
<tr>
<td>Microbial limits</td>
<td>· Formulation · Raw materials · Process parameters · Scale/equipments · Site</td>
<td>L</td>
<td>Microbial testing will be performed on stability for three commitment stability batches.</td>
<td>L</td>
<td>None</td>
</tr>
<tr>
<td>Dissolution – BCS Class II &amp; IV</td>
<td>· Formulation · Raw materials · Exclude major reformulations · Process parameters · Scale/equipments · Site</td>
<td>M</td>
<td>Controlled for in specifications at with Q ~ (100) % at 45 minutes. Refer to Biopharm PMCs regarding validation of an HPLC method for dissolution testing, collection of data at 30 minutes and 45 minutes for commercial batches on stability, and collecting dissolution profiles at batch release.</td>
<td>M</td>
<td>Refer to Biopharm PMCs regarding validation of an HPLC method for dissolution testing, collection of data at 30 minutes and 45 minutes for commercial batches on stability, and collecting dissolution profiles at batch release.</td>
</tr>
</tbody>
</table>

*Risk ranking applies to product attribute/CQA
**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.