# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 208647Orig1s000

# PRODUCT QUALITY REVIEW(S)

**Recommendation: APPROVAL**

# NDA 208647
# Review 2

| | |
|---|---|
| Drug Name/Dosage Form | Rosuvastatin capsules |
| Strength | 5 mg, 10 mg, 20 mg, 40 mg |
| Route of Administration | Oral |
| Rx/OTC Dispensed | Rx |
| Applicant | Sun Pharma Global FZE |
| US agent, if applicable | NA |

| SUBMISSION(S) REVIEWED | DOCUMENT DATE | DISCIPLINE(S) AFFECTED |
|---|---|---|
| 0017 | 06/18/2018 | Complete Response |

**Quality Review Team**

| DISCIPLINE | PRIMARY REVIEWER | SECONDARY REVIEWER |
|---|---|---|
| Drug Product | Christopher Galliford | Danae Christodoulou |
| Facility | Donald Lech | Brian Ryan |
| Regulatory Business Process Manager | Anika Lalmansingh | Hamet Toure |
| Application Technical Lead | Christopher Galliford | Danae Christodoulou |

# Quality Review Data Sheet

## 1. RELATED/SUPPORTING DOCUMENTS

### A. DMFs:

| DMF # | Type | Holder | Item Referenced | Status | Date Review Completed | Comments |
|---|---|---|---|---|---|---|
| (b) (4) | Type II | (b) (4) | Rosuvastatin calcium | adequate | 4/5/15/16 | by S. Bain/D. Christner |

**B. Other Documents:** none

**C. CONSULTS:** none

# Executive Summary

## I. Recommendations and Conclusion on Approvability

The recommendation from the Office of Pharmaceutical Quality (including the Overall Manufacturing Inspection Recommendation) is for **APPROVAL**.

## II. Summary of Quality Assessments

### A. Product Overview

This is a 505(b)(1) application but not for an New Molecular Entity. The active ingredient has several approved NDAs. The original submission in 08/28/2015 received a complete response for deficiencies found in the facilities inspection. These deficiencies are summarized below:

*Summary of Complete Response issues from the complete response letter:*
*Sun Pharmaceutical Industries Limited, Halol-Baroda 389350, Gujarat, India, is the proposed drug product manufacturer. This site was most recently inspected in September 2014. Numerous cGMP deficiencies were identified and FDA issued a warning letter on 12/17/2015. To date, the deficiencies have not been resolved.*

*Action letter language:*
*"During a recent inspection of Sun Pharmaceutical Industries Limited, Halol-Baroda 389350, Gujarat, India, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved."*

*In the resubmitted NDA, updates for this facility include a GMP inspection completed 3/9/2018 classified VAI, and a Pre-Approval Inspection (PAI) completed 6/23/2016 classified VAI. The facilities reviewer found the firms used in the manufacturing process and quality testing to be acceptable and recommended approval based on the updated information on 10/9/2018.*

| | |
|---|---|
| **Proposed Indication(s) including Intended Patient Population** | Rosuvastatin is approved for the treatment of primary hyperlipidemia and mixed dyslipidemia as an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-C, and TG levels and increased HDL-C. |
| **Duration of Treatment** | chronic |
| **Maximum Daily Dose** | 40 mg |
| **Alternative Methods of Administration** | not applicable |

The labeling review was completed with no major changes. The applicant accepted all proposed changes from the clinical team. Refer to the overall quality summary # 1 for further discussion of the labeling.

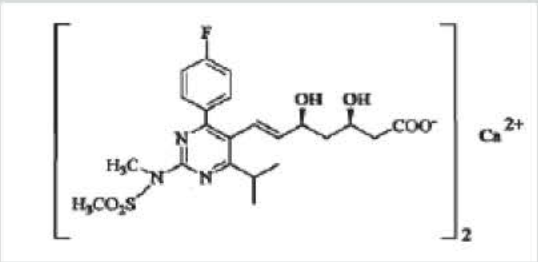
## B. Quality Assessment Overview

There are minimal changes to the drug substance, drug product, dosage form or route of administration in the resubmitted application. A brief description of the drug substance and drug product are summarized below along with the evaluation of a risk assessment f*or elemental impurities provided by applicant. See also Review 1 overall quality assessment:*

***Drug Substance***

Chemical Name or IUPAC Name/Structure:

*Rosuvastatin calcium*
(3R, 5S)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidin-5-yl]-3,5-dihydroxy-6(E)-heptenoic acid calcium salt (2:1)
Molecular formula: C44H54F2N6O12S2•Ca
Molecular weight: 1001.14 (salt)/963.08 (base)




Rosuvastatin calcium is an off-white to light yellow colored powder. It is insoluble in water and soluble in *N,N*-dimethyl formamide, acetone, and acetonitrile.

***Drug Product***

The drug product comprises hard gelatin capsules filled with rosuvastatin calcium granules. The active pharmaceutical ingredient, rosuvastatin calcium is already commercially available in a daily 5, 10, 20 and 40 mg tablet formulation approved in 2003 under NDA (b) (4). The capsule dosage form is designed with the advantage of

being administered by sprinkling the capsule contents on a spoonful of soft food such as apple sauce for patients who have difficulty in swallowing.
product is a gelatin capsule containing the immediate-release drug granules, for oral administration as a whole capsule or as sprinkles on apple sauce, or for administration via nasogastric tubing as an aqueous suspension. The proposed dosage strengths are 5, 10, 20, and 40 mg rosuvastatin free-acid. The different strengths differ by the amount of granules per capsule and the capsule shell size. The (b) (4) size is stated to be (b) (4) microns to meet FDA's guidelines on this type of dosage form.

- Rosuvastatin capsules 5 mg are hard gelatin capsule, Size "3" pink cap/off white body, imprinted axially with "984" on cap and body in black ink filled with yellow colored granules.
- Rosuvastatin capsules 10 mg are hard gelatin capsule, Size "3" purple cap/off white body, imprinted axially with "985" on cap and body in black ink filled with yellow colored granules.
- Rosuvastatin capsules 20 mg are hard gelatin capsule, Size "1" blue cap/off white body, imprinted axially with "986" on cap and body in black ink filled with yellow colored granules.
- Rosuvastatin capsules 40 mg are hard gelatin capsule, Size "0el" green cap/white body, imprinted axially with "987" on cap and body in black ink filled with yellow colored granules.

Excipients are microcrystalline cellulose, crospovidone, mannitol, magnesium oxide, ferric oxide, sodium citrate, hypromellose, polyethylene glycol, and silicon dioxide. Components of the gelatin capsule include titanium dioxide, gelatin, water, and sodium lauryl sulfate. Additionally following colorants are used in capsules: FD & C Red 40 (5 mg), FD & C Blue 1 (5 mg, 10 mg, 20 mg), D & C Red 28 (5 mg, 10 mg), FD & C Red 3 (20 mg), and FD & C Green 3 (40 mg). The imprinting black ink contains shellac, butyl alcohol, propylene glycol, strong ammonia solution, black iron oxide and potassium hydroxide. Gelatin is (b) (4) are included in the NDA.

***Manufacturing Process:***
The product manufacturing process consists of (b) (4)
(b) (4)

***Container Closure***
HDPE bottles with child resistant (b) (4) closures.

***Expiration Date & Storage Conditions:***
24 months at room temperature for all three commercial container closure systems. The primary stability batches and the commercial product have the same formulation (with the exception of the capsule printing) and comparable container closure systems. The

primary stability batches were manufactured at the commercial site using a commercial-comparable process, (b) (4), and one of the batches was the 40 mg batch JKN2312 used in the pivotal BE studies 14128 and 14129.

In addition, the applicant has also updated Section 3.2.P.2 to include a risk assessment for elemental impurities per ICH Q3D. As per the risk assessment report, levels of all potential elements in drug product are well below the controlled threshold (b) (4) hence no further control of elemental impurities in the drug product is acceptable.

**C. Special Product Quality Labeling Recommendations (NDA only)**

Not applicable

**D. Final Risk Assessment (see Attachment)**

***Application Technical Lead Name and Date:***

***Christopher Galliford, 12/17/2018***

Christopher Galliford -S

Digitally signed by Christopher Galliford -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001708703, cn=Christopher Galliford -S
Date: 2018.12.18 09:42:12 -05'00'

## QUALITY ASSESSMENT

Attachment

| From Initial Risk Identification | | | Review Assessment | | |
|---|---|---|---|---|---|
| **Attribute/ CQA** | **Factors that can impact the CQA** | **Initial Risk Ranking** | **Risk Mitigation Approach** (b) (4) | **Final Risk Evaluation** | **Lifecycle Considerations/ Comments** |
| Drug content/Assay | Formulation<br>Process<br>Container closure | H | | L | none |
| Impurities/ degradants | Formulation<br>Process<br>Container closure | H | | L | none |
| Appearance | Formulation<br>Process<br>Container closure | H | | L | none |
| Drug release rate | Formulation<br>Process | H | | L | reference the pharmaceutical development for any change in formulation or process |
| Content uniformity | Process | H | | L | evaluate any change in the specific process steps |

7 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

**Recommendation:**
**Complete Response**
**(including the Facility Review/Manufacturing Inspection Recommendation)**

# NDA 208647
# Review #1
# Review Date (see page 6)

| | |
|---|---|
| **Drug Name/Dosage Form** | Rosuvastatin capsule |
| **Strength** | 5, 10, 20, and 40 mg free-acid |
| **Route of Administration** | oral |
| **Rx/OTC Dispensed** | Rx |
| **Applicant** | Sun Pharma |

| SUBMISSION(S) REVIEWED | DOCUMENT DATE |
|---|---|
| 0000 | 8/28/15 |
| 0006 | 11/27/15 |
| 0013 | 2/5/16 |
| 0014 | 3/2/16 |
| 0015 | 4/22/16 |

**Quality Review Team**

| DISCIPLINE | REVIEWER | DIVISION/OFFICE |
|---|---|---|
| Application Technical Lead | Suong Tran | New Drug Products I/ONDP |
| Regulatory Business Process Manager | Anika Lalmansingh | Regulatory Business Process Management I/OPRO |
| Drug Substance | Sam Bain | New Drug API/ONDP |
| Drug Product | Christopher Galliford | New Drug Products II/ONDP |
| Biopharmaceutics | Peng Duan | Biopharmaceutics/ONDP |
| Process | Haitao Li | Process Assessment II/OPF |
| Microbiology | Haitao Li | Process Assessment II/OPF |
| Facility | Donald Lech | Inspectional Assessment/OPF |

## Quality Review Data Sheet

1. **RELATED/SUPPORTING DOCUMENTS:**
   A. **DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | STATUS[1] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|
| (b) (4) | II | (b) (4) | Rosuvastatin calcium | adequate | 4/15/16 | by S. Bain/D. Christner |

For the following Type III DMFs:
Adequate information provided in the NDA (by C. Galliford/D. Christodoulou).

| Type | Description | Supplier | DMF # |
|---|---|---|---|
| Bottle (30 cc) | | | (b) (4) |
| Bottles (75 cc, 120 cc) | | | |
| Bottle (60 cc) | | | |
| Bottle (180 cc) | | | |
| Caps | | | |
| Closure Liner | | | |

(b) (4)

| Type | Description | Supplier | DMF # |
|---|---|---|---|
| Hard gelatin capsule shells | Hard gelatin capsule shells (size "3") pink/off white | | (b) (4) |
| | Hard gelatin capsule shells (size "3") purple/off white | | |
| | Hard gelatin capsule shells (size "1") blue/off white | | |
| | Hard gelatin capsule shells (size "0EL") green/white | | |

B. **Other Documents:** none

2. **CONSULTS:** none

# Executive Summary

## I. Recommendation

The recommendation from the Office of Pharmaceutical Quality (including the manufacturing inspection recommendation) is for a **Complete Response** (see issues below).

Labeling comments will be finalized during the multi-disciplinary OND-managed labeling review.

### A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues: Sun Pharmaceutical Industries Limited, Halol-Baroda 389350, Gujarat, India, is the proposed drug product manufacturer. This site was most recently inspected in September 2014. Numerous cGMP deficiencies were identified and FDA issued a warning letter on 12/17/2015. To date, the deficiencies have not been resolved.
2. Action letter language: "During a recent inspection of Sun Pharmaceutical Industries Limited, Halol-Baroda 389350, Gujarat, India, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved."

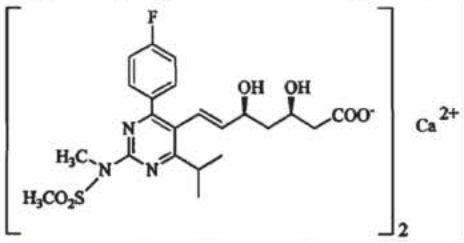
### B. Recommendation on Post-Marketing Commitments, Agreements, and/or Risk Management Steps- not applicable

## II. Summary of Quality Assessment

This is a 505(b)(2) application for a new dosage form of rosuvastatin (oral capsule), that relies on FDA's findings of safety and efficacy for NDA 21366 Crestor (rosuvastatin calcium) Tablets.

### A. Drug Substance

The chemical name for rosuvastatin calcium is bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidin-5-yl]-(3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt with the following structural formula:




The molecular formula for rosuvastatin calcium is $(C_{22}H_{27}FN_3O_6S)_2 \cdot Ca$ and the molecular weight is 1,001.14. Rosuvastatin calcium is off-white to light yellow amorphous powder that is slightly soluble in water and methanol, and insoluble in

ethanol. Rosuvastatin calcium is a hydrophilic compound with a partition coefficient (octanol/water) of 0.13 at pH of 7.

DMF (b) (4) is referenced for all CMC information on the drug substance. The DMF was found adequate to support this NDA on 4/15/2016 by ONDP/DNDAPI (E. Englund/D. Christner).

## B. Drug Product

The product is a gelatin capsule containing the immediate-release drug granules, for oral administration as a whole capsule or as sprinkles on apple sauce, or for administration via nasogastric tubing as an aqueous suspension. The proposed dosage strengths are 5, 10, 20, and 40 mg rosuvastatin free-acid. The different strengths differ by the amount of granules per capsule and the capsule shell size. The (b) (4) size is stated to be (b) (4) microns to meet FDA's guidelines on this type of dosage form.

- Rosuvastatin capsules 5 mg are hard gelatin capsule, Size "3" pink cap/off white body, imprinted axially with "984" on cap and body in black ink filled with yellow colored granules.
- Rosuvastatin capsules 10 mg are hard gelatin capsule, Size "3" purple cap/off white body, imprinted axially with "985" on cap and body in black ink filled with yellow colored granules.
- Rosuvastatin capsules 20 mg are hard gelatin capsule, Size "1" blue cap/off white body, imprinted axially with "986" on cap and body in black ink filled with yellow colored granules.
- Rosuvastatin capsules 40 mg are hard gelatin capsule, Size "0el" green cap/white body, imprinted axially with "987" on cap and body in black ink filled with yellow colored granules.

Excipients are microcrystalline cellulose, crospovidone, mannitol, magnesium oxide, ferric oxide, sodium citrate, hypromellose, polyethylene glycol, and silicon dioxide. Components of the gelatin capsule include titanium dioxide, gelatin, water, and sodium lauryl sulfate. Additionally following colorants are used in capsules: FD & C Red 40 (5 mg), FD & C Blue 1 (5 mg, 10 mg, 20 mg), D & C Red 28 (5 mg, 10 mg), FD & C Red 3 (20 mg), and FD & C Green 3 (40 mg). The imprinting black ink contains shellac, butyl alcohol, propylene glycol, strong ammonia solution, black iron oxide and potassium hydroxide.

(b) (4)

The product manufacturing process consists of (b) (4)

(b) (4)

The drug product specification includes attributes standard for the dosage form. Water content has a stability limit of (b)(4)% due to (b) (4)

Limits on degradants meet the applicable ICH identification and qualification threshold for the maximum daily dose of (b)(4) mg, with the exception of (b) (4)

Container Closure systems: 30-count and 90-count HDPE bottles with desiccant and child-resistant closures, and foil blisters

Expiration Date & Storage Conditions: 24 months at room temperature for all three commercial container closure systems.

The primary stability batches and the commercial product have the same formulation (with the exception of the capsule printing) and comparable container closure systems. The primary stability batches were manufactured at the commercial site using a commercial-comparable process, at (b) (4) and one of the batches was the 40 mg batch JKN2312 used in the pivotal BE studies 14128 and 14129.

## C. Summary of Drug Product Intended Use

| | |
|---|---|
| **Proprietary Name** | none |
| **Non Proprietary Name of the Drug Product** | rosuvastatin capsule |
| **Non Proprietary Name of the Drug Substance** | rosuvastatin calcium |
| **Proposed Indication(s)** | [not finalized by GRMP goal; see CDTL's memo – Division of Metabolism and Endocrinology Products |
| **Duration of Treatment** | chronic |
| **Maximum Daily Dose** | 40 mg |
| **Alternative Methods of Administration** | Adequate compatibility studies are provided for the use of drug granules as sprinkles on apple sauce and as an aqueous suspension for the nasogastric administration. |

## D. Biopharmaceutics Considerations

The 40 mg batch JKN2312 used in the pivotal BE studies 14128 and 14129 and the commercial product have the same formulation (with the exception of the capsule printing). The different strengths of 5 mg, 10 mg, 20 mg, and 40 mg are composition-proportional and their dissolution profiles are sufficiently similar. Therefore, the biowaiver request for the lower strengths 5 mg, 10 mg, and 20 mg is acceptable provided that the BA/BE results are found acceptable for the 40 mg strength and Crestor, the listed drug relied upon; reference is made to the Clinical Pharmacology review for details and conclusion.

Adequate dissolution data are provided in support of the use of drug granules as sprinkles on apple sauce (within 60 minutes at room temperature) and as an aqueous suspension for the nasogastric administration (within 90 minutes at room temperature, dispersed in water, and using (b) (4) (16-French) tubing). Adequate data have been provided in support of the dissolution test method and acceptance.

**E. Novel Approaches**: not applicable
**F. Any Special Product Quality Labeling Recommendations**: not applicable
**G. Life Cycle Knowledge Information (see Attachment)**

## OVERALL ASSESSMENT AND SIGNATURE: EXECUTIVE SUMMARY

**Application Technical Lead Signature:**
**I concur with the reviewers' conclusions.**

Suong T. Tran -S

Digitally signed by Suong T. Tran -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Suong T. Tran -S, 0.9.2342.19200300.100.1.1=1300101829
Date: 2016.05.18 14:50:22 -04'00'

**Suong (Su) Tran, PhD, Quality/CMC Lead, OPQ**

## ASSESSMENT OF THE BIOPHARMACUETICS

1. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

The proposed rosuvastatin capsules are an immediate release product in 5, 10, 20, and 40 mg strengths, which are (b) (4) (Table 1). It is a hard gelatin capsule filled with drug-containing (b) (4), designed to facilitate dosing in patients with swallowing problem. It may be swallowed intact or the content can be sprinkled onto a soft food. It can also be administrated via a nasogastric tube.

**Table 1. Rosuvastatin Capsules Composition**

| Ingredient | Function | mg/capsule (b) (4) | | | |
|---|---|---|---|---|---|
| | | 5 mg Capsule | 10 mg Capsule | 20 mg Capsule | 40 mg Capsule |
| (b) (4) | | | | | |
| Rosuvastatin calcium# | API | 5.198 | 10.395 | 20.790 | 41.580 |
| Microcrystalline cellulose NF/Ph. Eur. (b) (4) | | | | | (b) (4) |
| Crospovidone NF/Ph. Eur. (b) (4) | | | | | |
| Mannitol USP/Ph. Eur. (b) (4) | | | | | |
| Magnesium oxide USP (b) (4) | | | | | |
| Ferric oxide (b) (4) NF (b) (4) | | | | | |
| Sodium Citrate USP/Ph. Eur. (b) (4) (b) (4) | | | | | (b) (4) |
| | | | | | (b) (4) |
| Hypromellose USP/Ph. Eur (b) (4) | | | | | (b) (4) |
| Polyethylene Glycol 4000 NF/ (b) (4) | | | | | |
| Isopropyl alcohol USP/Ph. Eur.* | | | | | |
| Purified water, USP* (b) (4) | | | | | |
| Silicon dioxide NF (b) (4) (b) (4) (b) (4) | | | | | |
| **Capsule filling** | | | | | |
| Hard gelatin capsule shells (b) (4) | | | | | |
| **Capsule Shell Description** | -- | EHG Capsule size '3' pink/off white** | EHG Capsule size '3' purple/off white** | EHG Capsule size '1' blue/off white** | EHG Capsule size '0 El' green/ white** |

*Not present in final formulation
** 5mg - Axially imprinted with '984' on cap and body in black ink
10mg - Axially imprinted with '985' on cap and body in black ink
20mg - Axially imprinted with '986' on cap and body in black ink
40mg - Axially imprinted with '987' on cap and body in black ink
#Rosuvastatin calcium equivalent to Rosuvastatin 5, 10, 20 and 40 mg, respectively

(b) (4)

The proposed dissolution method is shown in Table 2, which is the same recommended by the Agency.

**Table 2. Proposed dissolution method for rosuvastatin capsules**

| | |
|---|---|
| **Dissolution Medium** | pH 6.6, 0.05M sodium citrate buffer |
| **Volume** | 900 mL |
| **Apparatus** | USP Apparatus II (Paddle) |
| **Speed** | 50 rpm |
| **Sampling Times** | 5, 10, 15, 20, 30, 45 minutes |
| **Proposed specification** | Not less than (b) (4)% (Q) of label claim in 20 minutes.<br>For release at S1, no individual unit is less than (b) (4)% of label claim in 20 minutes.<br>For release at S2, average of 12 units is equal to or greater than (b) (4)% of label claim and no individual unit is less than (b) (4)% of label claim in 20 minutes.<br>For release at S3, average of 24 units is equal to or greater than (b) (4)% of label claim and not more than 2 units are less than (b) (4)% of label claim and no unit is less than (b) (4)% of label claim in 20 minutes. |
| **Detection** | HPLC, at (b) (4) nm |

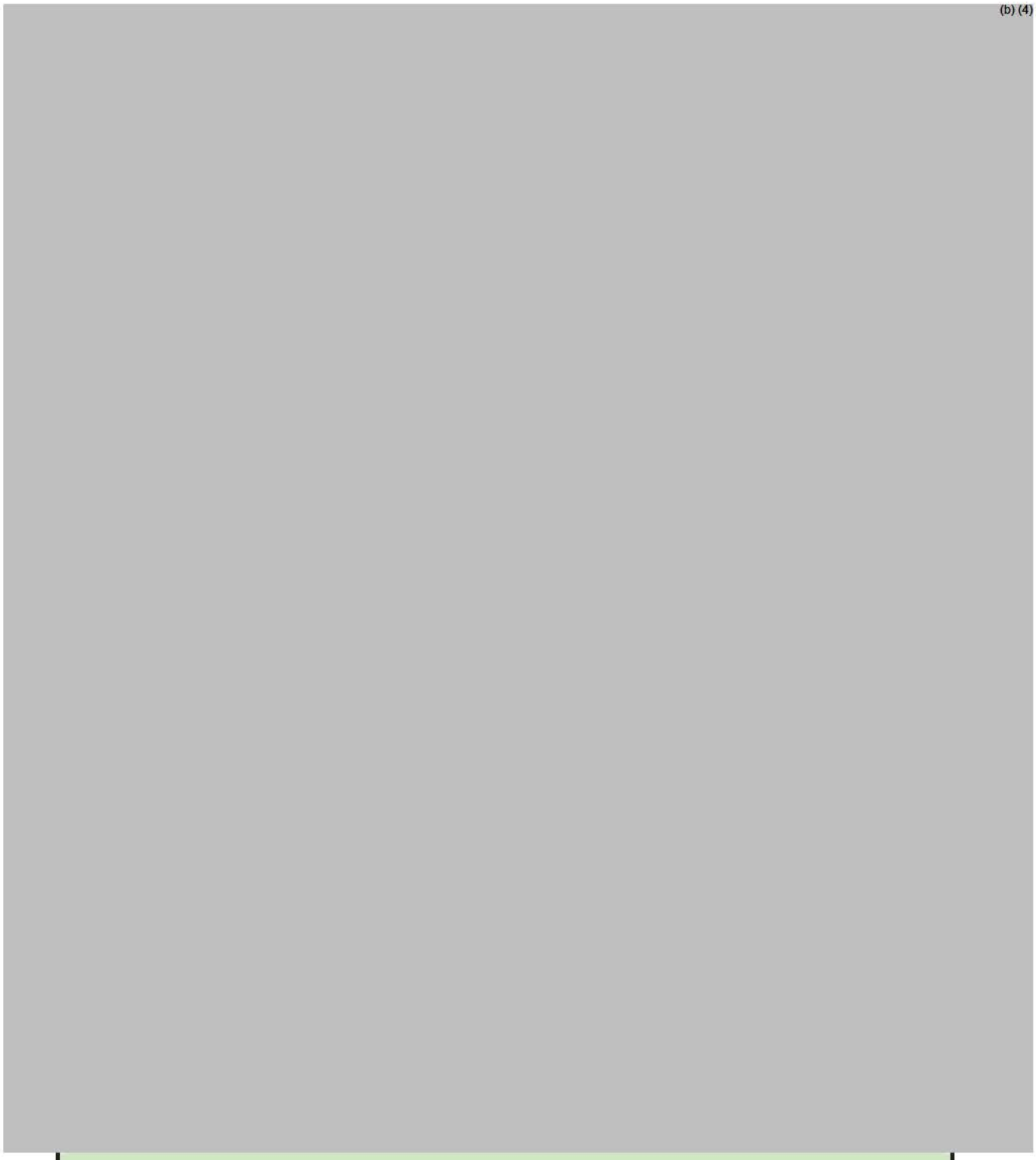
Source: 8.2, Specification 0012570 Rev. 9.0

**Reviewer's Assessment:**

**1. Dissolution method**

(b) (4)

3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

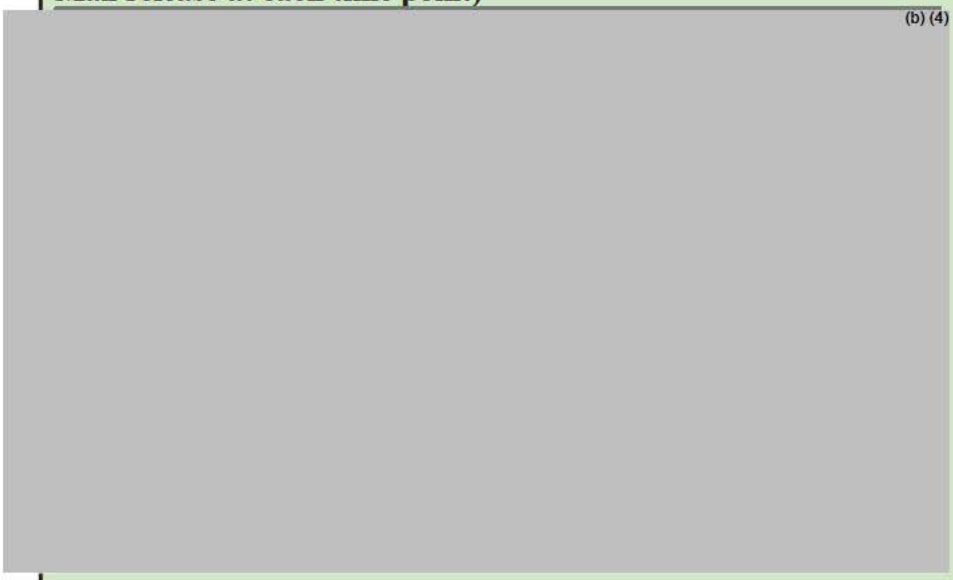



**1.6 Dissolution acceptance criterion**

The proposed dissolution acceptance criterion is Q= (b) (4) % in 20 min. Figure 6 shows the comparative dissolution profiles of different strengths of proposed rosuvastatin capsules 5mg, 10 mg, 20 mg, and 40 mg with proposed dissolution method.

**Figure 6. Comparative dissolution of rosuvastatin capsules 5 mg, 10 mg, 20 mg, and**

**40 mg in pH 6.6, 0.05 M Citrate Buffer (QC Method) (Error bar represents Min and Max release at each time point)**

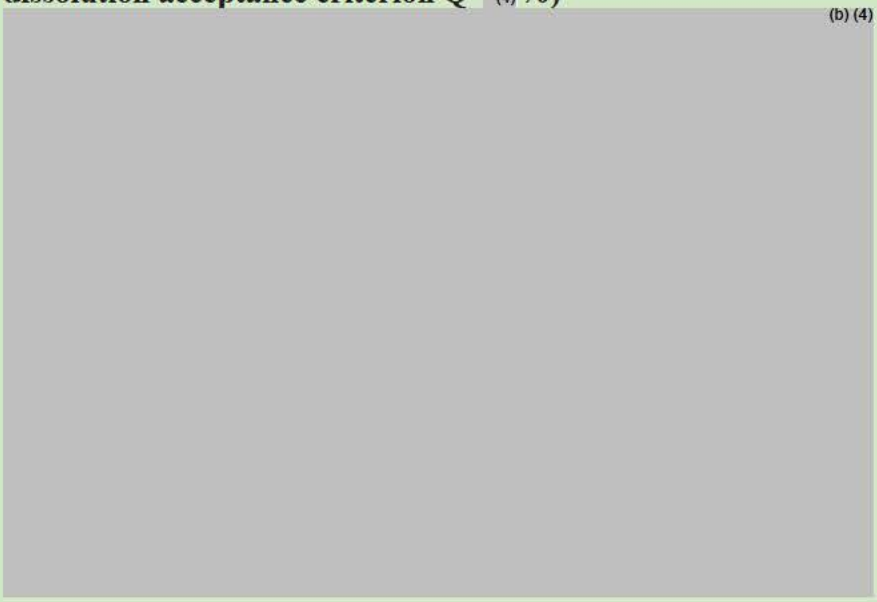



As Figure 6 shows, the dissolution profiles of different strengths of rosuvastatin capsules are similar, and drug release in all of the strengths is higher than (b) (4)% and reaches plateau after time point of 20 min. and met the acceptance criterion ( (b) (4) (b) (4) Therefore, setting Q as (b) (4)% in 20 min seems reasonable.

Figure 7 shows the batch analysis of drug release at 20 min for batches of rosuvastatin 5 mg (# JKN2372, JKN2373 and JKN 2374), 10 mg (# JKN 2369, JKN2370, and JKN2371), 20 mg (# JKN2313, JKN2314, and JKN2315), and 40 mg(# JKN2310, JKN2311, and JKN 2312). Samples from these batches have been placed on stability test at room temperature 25°C/60% RH up to 36 months or at intermediate condition 30°C/65% RH up to 12 months or at accelerated condition 40°C/75% RH up to 6 months.

**Figure 7. Drug release at 20 min for each strength of rosuvastatin capsules ( Mean,**

**Min, and Max from three batches of each strength; redline represents proposed dissolution acceptance criterion Q= (b) (4) %)**




As Figure 7 shows, the units tested for all strengths met the proposed dissolution acceptance criterion Q= (b) (4) % in 20 min. Furthermore, no significant difference was found for the drug release during stability test across all strengths.

Overall, the proposed dissolution acceptance criterion Q= (b) (4) % in 20 min is acceptable.

**1.7. Dissolution analytical method validation**

The analytical method for dissolution is following the HPLC. The summary for the dissolution method is shown in Table 4.

**Table 4. chromatographic (High Performance Liquid Chromatograph (HPLC)) conditions for dissolution method**

| | |
|---|---|
| **Mobile Phase** | **Buffer**<br>Transfer about 8.19 g of Citric acid anhydrous accurately weighed to a 1000 mL volumetric flask, dissolve in about 900 mL of water, adjust with 25 % Ammonia solution to a pH 2.50 ± 0.05, dilute with water to volume. Mix and filter through 0.45µ filter.<br>**Mobile Phase**<br>Add graduate measured 700 mL Buffer, 200 mL Acetonitrile and 100 mL Tetrahydrofuran. Mix well and degas to avoid air bubble formation. |
| **Column** | L1, 4.6 x 50 mm, 3.5µ; Waters Symmetry C18, 50 x 4.6mm, 3.5µ |
| **Detector** | UV at 248 nm |
| **Flow Rate** | 1.0 mL per minute |
| **Sample Cooler temperature** | 10°C |
| **Column Oven Temperature** | 25°C |
| **Injection Volume** | 50 µL |
| **Injection Rinse port** | Water: Acetonitrile (20: 80, %v/v) |
| **Run time** | About 20 min |
| **Retention time** | **Rosuvastatin** : About 8.5 min |
| **System Suitability** | The relative standard deviation for five replicate injections of standard preparation of Rosuvastatin should be not more than (b) (4)%, the tailing factor should be not less than (b) (4) and not more than (b) (4) and plate counts should be not less than (b) (4) |

The dissolution method has been validated for specificity, precision, accuracy, linearity, stability of analytical solution and robustness according to validation report # CAL/AMVR/15/0174. The validation report is acceptable. Table 5 shows the summary for the validation report of dissolution analytical method.

**Table 5. Validation Summary**

| | |
|---|---|
| **Specificity** | Rosuvastatin peak is well separated from any peak due to Blank, Placebo and any other peaks. |
| **Linearity** | **With out pepsin:**<br>0.055 µg/ml to 66.245 µg/ml (1% to 1200% of target concentration)<br>Correlation coefficient (r) = 1.0000<br>**With pepsin:**<br>0.055 µg/ml to 66.245 µg/ml (1% to 1200% of target concentration)<br>Correlation coefficient (r) = 1.0000 |
| **Range** | 2.255 µg/ml to 66.245 µg/ml (40.047% to 1192.315% of sample concentration) |
| **System precision** | The %RSD of area of Rosuvastatin peak from five replicate injections of Standard preparation is 0.08 %. |
| **Method precision** | After 30 minutes, %RSD of % dissolved of Rosuvastatin from six Sample aliquot from same vessel is 0.00 %.<br><br>After 30 minutes, Mean of % dissolved of Rosuvastatin from six Samples preparation from different vessel is 106%.<br><br>**With pepsin:**<br>After 30 minutes, %RSD of % dissolved of Rosuvastatin from six Sample aliquot from same vessel is 0.81%.<br><br>After 30 minutes, Mean of % dissolved of Rosuvastatin from six Samples preparation from different vessel is 104%. |

| | |
|---|---|
| **Intermediate Precision** | After 30 minutes, %RSD of % dissolved of Rosuvastatin from six Sample aliquots from same vessel is 0.00 %.<br><br>After 30 minutes, mean of %dissolved of Rosuvastatin from six Sample preparations from different vessels is 103 %.<br><br>Difference in Mean value of drug release of Rosuvastatin from six individual vessels after 30 minutes between Intermediate Precision 103 % and Method Precision 106 % = -3%.<br><br>**With pepsin:**<br>After 30 minutes, %RSD of % dissolved of Rosuvastatin from six Sample aliquots from same vessel is 0.00 %.<br><br>After 30 minutes, mean of %dissolved of Rosuvastatin from six Sample preparations from different vessels is 104 %.<br><br>Difference in Mean value of drug release of Rosuvastatin from six individual vessels after 30 minutes between Intermediate Precision 104 % and Method Precision 104 % = 0%. |

| **Accuracy** | **Rosuvastatin (Without pepsin)** | |
|---|---|---|
| | **% Recovery** | **% RSD** |
| **40%** | 98.5-98.8 | 0.15 |
| **100%** | 100.3-100.4 | 0.06 |
| **1200%** | 99.6-99.8 | 0.12 |
| **Accuracy** | **Rosuvastatin (With pepsin)** | |
| | **% Recovery** | **% RSD** |
| **40%** | 99.7-99.9 | 0.10 |
| **100%** | 99.5-99.7 | 0.10 |
| **1200%** | 99.7-99.8 | 0.06 |

| | |
|---|---|
| **Solution stability** | Standard preparation: 37 hrs. at 10°C temperature.<br>Sample preparation: 36 hrs. at 10°C temperature.<br>Sample preparation (With pepsin): 32 hrs. at 10°C temperature. |
| **Robustness** | **Acceptance Criteria:**<br>%RSD of area of Rosuvastatin peak from five replicate injections of Standard preparation: NMT (b) (4)%.<br><br>The tailing factor should not be less than (b) (4) and not more than (b) (4) for Rosuvastatin peak.<br>Plate counts should not be less than (b) (4) for Rosuvastatin peak |
| | Following variations in chromatographic parameters comply with above mentioned acceptance criteria.<br><br>Flow rate: ± 0.2 mL/min<br>Column oven temperature: ± 2°C<br>Wavelength: ± 2 nm<br>Concentration of Acetonitrile: ± 5% v/v (absolute)<br>pH of Buffer : ± 0.2 unit |

The original dissolution method was developed and validated in Sun Pharmaceuticals Advanced Research Company in Mumbai. Later, it was transferred to Sun Pharmaceuticals Industries Limited in Halol. An analytical method transfer report for dissolution was submitted to support this technology transfer, and was acceptable.

## 2. In-use study of rosuvastatin capsules 40 mg in apple sauce

The Applicant conducted a study of sprinkling rosuvastatin 5mg and 40 mg capsules in applesauce, which was to support instructions that the drug product may be sprinkled onto soft food before ingestion. The capsule was opened, and then the (b) (4) was sprinkled on apple sauce and kept at room temperature for 10, 30, and 60 min.

The pH measurement was carried on three in-use applesauce samples of both 5 mg and 40 mg strengths of capsules, and the pH of applesauce/ (b) (4) mixtures was increased slightly (~30%) after 60 min at room temperature (Table 4).

**Table 4. The pH values of in-use rosuvastatin (b) (4) /applesauce samples**

| Sr. No. | Applesauce | Rosuvastatin (b) (4) applesauce mixture | | | |
|---|---|---|---|---|---|
| | | JKN2372 (5 mg) | | JKN2312 (40 mg) | |
| | | at 0 minute | after 60 minutes | at 0 minute | after 60 minutes |
| 1 | 3.32 | 3.41 | 3.58 | 3.85 | 4.74 |
| 2 | 3.33 | 3.44 | 3.62 | 3.80 | 4.70 |
| 3 | 3.31 | 3.43 | 3.60 | 3.82 | 4.72 |
| **Mean** | **3.32** | **3.43** | **3.60** | **3.82** | **4.72** |
| **Testing date** | 10-Jul-2015 | | | | |
| **LNB ref[1]** | SL1537-22 | | | | |

[1]Lab notebook reference

Figure 6 shows the dissolution profiles of intact capsule (control) and (b) (4) sprinkled onto applesauce for 10 min, 30 min, and 60 min for 5 mg and 40 mg rosuvastatin capsules.

**Figure 6A. Comparative mean dissolution profiles of intact Rosuvastatin capsules, 5 mg and rosuvastatin (b) (4) /applesauce mixture at various storage periods**

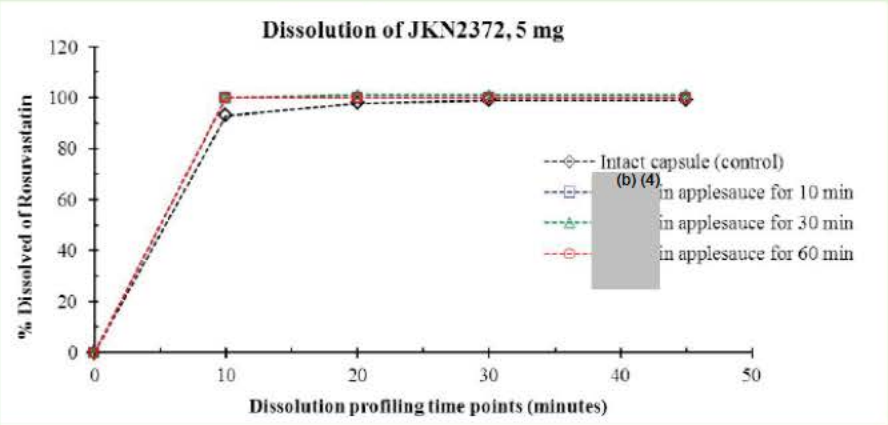
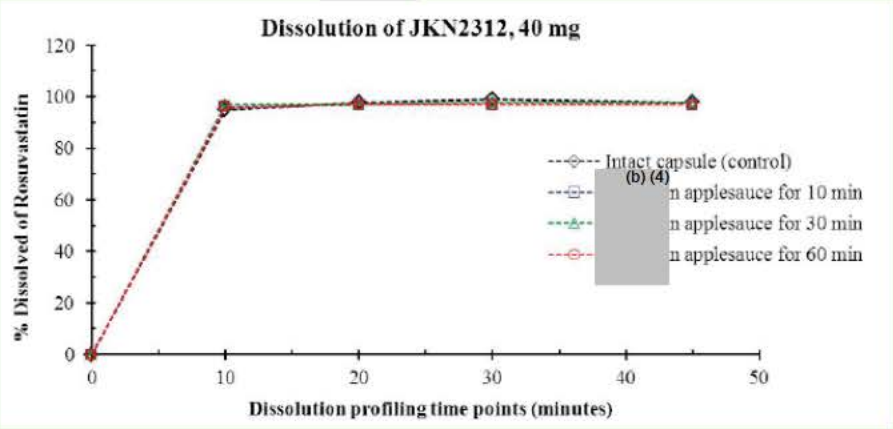



**Figure 6B. Comparative mean dissolution profiles of intact Rosuvastatin capsules,**

**40 mg and rosuvastatin [(b) (4)] applesauce mixture at various storage periods**




Therefore, the dissolution profiles of both 5 mg and 40 mg capsule strengths sprinkled onto applesauce after various times were similar and not changed much. Mean % dissolved of rosuvastatin from [(b) (4)] /applesauce mixture were comparable to that from intact capsules for all storage periods (10, 30, and 60 min), and the difference between them was less than 5% at 20, 30, and 45 min (slightly higher than 5% at 10 min).

The Applicant also evaluated the stability of drug substance (assay of rosuvastatin from rosuvastatin capsules in control and on one tablespoon of applesauce stored for 60 min). The mean assay value on rosuvastatin from both 5 mg and 40 mg capsule strengths of at 60 min with applesauce was similar (the difference was less than 5%) as the assay value obtained from [(b) (4)] /applesauce mixture from control sample.

The Applicant also conducted in-use related substances study on applesauce. Rosuvastatin was stable while sprinkled onto applesauce and remained for 60 min, and the results (% w/w impurities) of in-use applesauce samples were within specification and comparable to that of control samples.

Overall, the results of in-use-study of rosuvastatin on applesauce are acceptable, and the time of 60 min is suitable for the consumption of rosuvastatin [(b) (4)] /applesauce mixture after sprinkling [(b) (4)] on applesauce.

**3. In vitro nasogastric tube study of rosuvastatin capsules 5 mg, 10 mg, 20 mg, and 40 mg**

In the proposed labeling, the Applicant states:

*"For patients who have a nasogastric tube in place, Rosuvastatin Capsules can be opened and the intact [(b) (4)] emptied into a 60-mL syringe and mixed with 40 mL of water. Replace the plunger and shake the syringe vigorously. The [(b) (4)] in Rosuvastatin Capsules may start dissolving which is acceptable. Attach the syringe to a nasogastric tube (≥16-French) and deliver the contents of the syringe through the nasogastric tube*

*into the stomach. After administering the* [(b) (4)]*, the nasogastric tube should be flushed with additional water. USE IN OTHER LIQUIDS* [(b) (4)] *IS THEREFORE NOT RECOMMENDED".*

To support the proposed labeling claim, the Applicant conducted an in vitro nasogastric (NG) tube study with rosuvastatin 5 mg and 40 mg capsules. The [(b) (4)] of one capsule were emptied into a 60-mL catheter tipped syringe, and then were suspended into 40 mL water. The syringe containing the suspended [(b) (4)] was kept at room temperature for various time periods 15, 30, 45, 60, and 90 min, and the suspended/dispersed [(b) (4)] were passed through a NG tube (16- French, [(b) (4)], and analyzed for dissolution, assay, and particle size.

The proposed QC dissolution method was applied for NG tube dissolution study. Figure 7 shows the comparative dissolution profiles of intact capsules and [(b) (4)] dispersion kept at RT for various periods in a catheter-tipped syringe and passed through a 16-French NG tube.

**Figure 7A. Comparative mean dissolution profiles of intact Rosuvastatin capsules, 5 mg and rosuvastatin [(b) (4)] dispersion incubated at RT for various storage periods in a catheter-tipped syringe and passed through a 16-French NG tube**

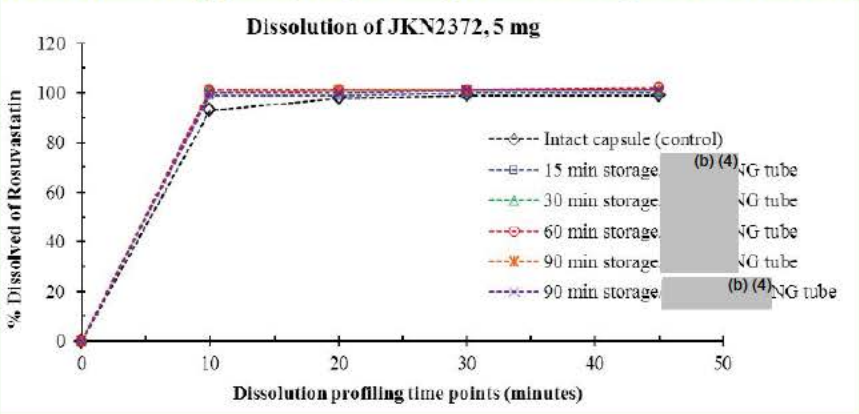
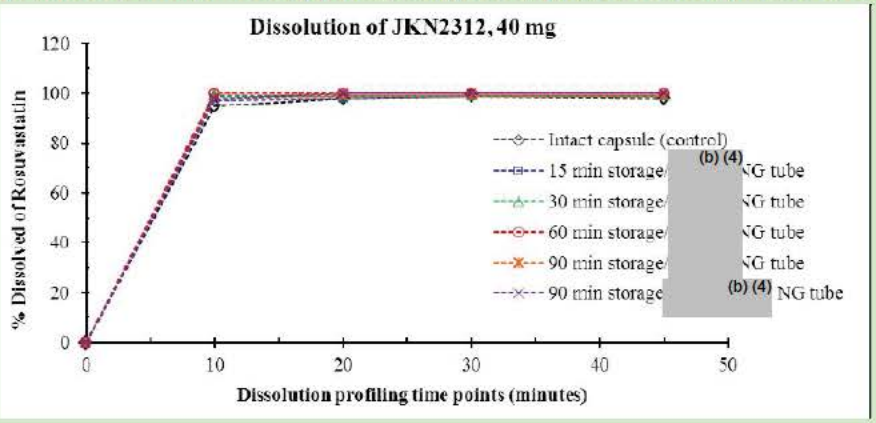



**Figure 7B. Comparative mean dissolution profiles of intact Rosuvastatin capsules,**

**40 mg and rosuvastatin (b) (4) dispersion incubated at RT for various storage periods in a cathetertipped syringe and passed through a 16-French NG tube**




As Figure 7 shows, mean % dissolved of rosuvastatin from (b) (4) dispersion were comparable to that from intact capsules for up to 90 min and the difference between them was less than 5% at specification time points ( 20, 30, and 45 min; slightly higher at 10 min). Both (b) (4) type of tubes (16-French) were suitable for nasogastric administration of rosuvastatin (b) (4) dispersed in water.

In the study of NG tube assay, mean assay value of rosuvastatin obtained from control samples (without NG tube/syringe) was no different as that from samples passed through NG tube/syringe (the difference was less than 5%) for both 5 mg and 40 mg strengths. Furthermore, the mean assay values of samples prepared from in vitro NG tube study lied between (b) (4) % for both 5 mg and 40 mg strengths, which met the acceptance criteria for assay.

In sedimentation study, at the end of 90 min, mean sedimentation depth was 1 mL for 5 mg and 4 mL for 40 mg (b) (4) dispersion. There was no difference in mean sedimentation depth for 5 mg strength from 0 to 90 min. However, for 40 mg strength, mean sedimentation depth was increased from 1 mL at 0 min to 4 mL at 90 min. The composition of 40 mg capsule is proportional to the composition of 5 mg capsules; therefore, the difference between 5 mg and 40 mg strengths in sedimentation study might be due to the larger number of (b) (4) present in the 40 mg strength.

The Applicant also evaluated particle size distribution of rosuvastatin (b) (4) dispersions of 5 mg and 40 mg strength (Table 8).

**Table 8A. Mean Particle size distribution of Rosuvastatin (b) (4) dispersion of**

**JKN2372, 5 mg**

| Storage period (minutes) | Mean particle size of rosuvastatin [redacted] dispersed in water (µm) | | | | | |
|---|---|---|---|---|---|---|
| | Passed through only syringe | | | Passed through [redacted] NG tube | | |
| | D10 | D50 | D90 | D10 | D50 | D90 |
| 0 | [redacted] | | | | | |
| 15 | | | | | | |
| 30 | | | | | | |
| 45 | | | | | | |
| 60 | | | | | | |
| 90 | | | | | | |

**Table 8B. Mean Particle size distribution of Rosuvastatin [redacted] dispersion of JKN2312, 40 mg**

| Storage period (minutes) | Mean particle size of rosuvastatin [redacted] dispersed in water (µm) | | | | | |
|---|---|---|---|---|---|---|
| | Passed through only syringe | | | Passed through [redacted] NG tube | | |
| | D10 | D50 | D90 | D10 | D50 | D90 |
| 0 | [redacted] | | | | | |
| 15 | | | | | | |
| 30 | | | | | | |
| 45 | | | | | | |
| 60 | | | | | | |
| 90 | | | | | | |

For 5 mg strength, there is [redacted] in the particle size for rosuvastatin [redacted] dispersion across all time points up to 90 min, whether pass through syringe or [redacted] NG tube. However, for 40 mg strength, the particle size for rosuvastatin [redacted] dispersion was [redacted] than that for 5 mg strength. [redacted]. The Applicant [redacted]

For the samples of 40 mg strength passed through only syringe, [redacted] observed for 90 minutes storage period compared to other storage periods, while the particle size [redacted] at different storage period in those passed through [redacted] NG tube.

Overall:

1. The NG tube dissolution data showed complete dissolution (recovery) of rosuvastatin when [redacted] of Rosuvastatin capsules, 5mg and 40 mg, were dispersed in 40 mL of water in a 60- mL catheter tipped syringe, incubated till 90 minutes at room temperature, and passed through a 16-French [redacted] NG tube.

2. Mean % dissolved of rosuvastatin from rosuvastatin (b) (4) dispersion are comparable to that from intact capsules for all storage periods studied (15, 30, 60, and 90 minutes).
3. Both (b) (4) type of NG tubes (16-French) are suitable for nasogastric administration of Rosuvastatin (b) (4) dispersed in water

**4. Biowaiver request**

**Evaluation: Acceptable**

Per the 21 CFR 320.22 (d)(2), a biowaiver may be granted if the drug product meets one of the following criteria:

1. The bioavailability of the drug product has been measured;
2. Both drug products meet an appropriate in vitro test approved by FDA; and
3. The applicant submits evidence showing that both drug products are (b) (4) (b) (4) in their active and inactive ingredients.

Similarly, per the requirements in ***Guidance for Industry: Dissolution testing of immediate release solid oral dosage forms***: for multiple strengths of IR products with linear kinetics, the bioequivalence study may be performed at the highest strength and waivers of in vivo studies may be granted on lower strengths, based on an adequate dissolution test, provided the lower strengths are (b) (4). The approval of additional strengths requires the similarity in dissolution profile comparisons between the strength employed in the bioequivalence study and additional strengths seeking biowaiver.

**4.1** (b) (4)

**Table 9. Qualitative and quantitative formulae of Rosuvastatin Capsules, 5 mg, 10 mg, 20 mg and 40 mg**

| Sr. No. | Item | Qty mg/Capsule (5 mg) | Qty mg/Capsule (10 mg) | Qty mg/Capsule (20 mg) | Qty mg/Capsule (40 mg) |
|---|---|---|---|---|---|
| 1 | Rosuvastatin Calcium | 5.1975 | 10.395 | 20.79 | 41.58 |
| 2 | Mycrocrystalline Cellulose | (b) (4) | | | |
| 3 | Crospovidone | | | | |
| 4 | Mannitol | | | | |
| 5 | Magnesium Oxide | | | | |
| 6 | Ferric Oxide | | | | |
| 7 | Sodium Citrate (b) (4) | | | | |
| 8 | PEG 4000 | | | | |
| 9 | Silicon dioxide | | | | |
| Average fill weight of the capsule | | | | | |

Table 9 shows the composition of different strengths of proposed rosuvastatin capsules. As evident from Table 9, rosuvastatin capsule 5mg, 10 mg, 20 mg, and 40 mg are

(b) (4)

**4.2 BA of rosuvastatin capsules 40 mg relative to the reference drug Crestor Tablets (NDA 021366) 40 mg**

The Applicant conducted two clinical bioavailability studies to compare the proposed 40 mg capsules to reference drug 40 mg tablets at fasting and fed conditions:

- Study PKD_14_128, A randomized, open label, three treatment, three period, six sequence, single dose, crossover relative bioavailability study in healthy adult males under fasting conditions
- Study PKD 14 129, A randomized, open label, three treatment, three period, six sequence, single dose, crossover relative bioavailability study in healthy adult males under fed conditions

Table 10 shows the PK parameters for rosuvastatin capsules 40 mg (Test) and reference drug rosuvastatin tablets 40 mg under fasting (Table 10A) and fed conditions (Table 10B).

**Table 10A: Mean (%CV) Pharmacokinetic Parameter Values and Ratio of Geometric Least-Square Mean Values of SPARC Ltd.'s Rosuvastatin Capsules, 40 mg, Intact (Test A) and Crestor® Tablets, 40 mg (Reference C) in Healthy Subjects Administered under Fasting Conditions (n = 41, Subject (b) (6) Excluded)**

| Parameter (Units) | Least Squares Geometric Means[3] (% CV[5]) | | Least Square Means Ratio Test/Reference[1] (90% CI)[2] | Intra Subject CV (%) |
|---|---|---|---|---|
| | Rosuvastatin Capsules, 40 mg Intact | Crestor® Tablets, 40 mg | | |
| $C_{max}$ (ng/mL) | 41.51 (51.1) | 42.47 (59.7) | 97.75 (89.67 – 106.55) | 23.36 |
| $AUC_{0-t}$ (ng·hr/mL) | 318.59 (53.3) | 341.10 (55.4) | 93.40 (87.14 – 100.11) | 18.72 |
| $AUC_{0-\infty}$ (ng·hr/mL) | 329.58 (52.4) | 353.87 (55.3) | 93.14 (86.83 – 99.90) | 18.92 |
| $T_{max}$ (hr)[4] | 2.33 (0.33 – 4.67) | 2.33 (0.33 – 5.00) | -- | -- |
| $T_{1/2}$ (hr)[5] | 10.88 (44.7) | 10.37 (62.2) | -- | -- |
| $K_{el}$ ($hr^{-1}$)[5] | 0.077 (47.9) | 0.080 (39.2) | -- | -- |

Source: PKD_14_128 Report, Table 4A and 4B

[1] Ratio of Least Square Means: calculated according to the formula: $e^{(\text{LSM Treatment (B)} - \text{LSM Treatment (A)})} \times 100$

[2] 90% Geometric Confidence Interval using Ln-transformed data

[3] Excluding data for subject (b) (6) (outlier)

[4] Median values (range) are presented for $T_{max}$

[5] Arithmetic mean values presented (n=43)

**Table 10B: Least Square Geometric Mean (%CV) Pharmacokinetic Parameter Values and Ratio of Geometric Least-Square Means Values of SPARC Ltd.'s Rosuvastatin Capsules, 40 mg, Intact and Crestor® (Rosuvastatin Calcium) Tablets, 40 mg in Healthy Subjects and Administered under Fed Conditions (n=45)**

| Parameter (Units) | Least Squares Geometric Means (% CV[4]) | | Least Square Means Ratio[1] Test/Reference (90% CI)[2] | Intra Subject CV (%) |
|---|---|---|---|---|
| | Rosuvastatin Capsules, 40 mg Intact | Crestor® Tablets, 40 mg | | |
| $C_{max}$ (ng/mL)[2] | 23.58 (48.8) | 21.23 (43.9) | 111.09 (102.58 – 120.31) | 22.75 |
| $AUC_{0-t}$ (ng·hr/mL)[2] | 202.70 (49.3) | 189.80 (55.6) | 106.80 (100.01 – 114.04) | 18.67 |
| $AUC_{0-\infty}$ (ng·hr/mL)[2] | 213.33 (47.9) | 200.40 (53.5) | 106.46 (100.10 – 113.22) | 17.50 |
| $T_{max}$ (hr)[3] | 5.67 (2.67 – 6.00) | 4.67 (0.33 – 5.67) | -- | -- |
| $T_{1/2}$ (hr)[4] | 10.29 (28.1) | 10.07 (35.0) | -- | -- |
| $K_{el}$ ($hr^{-1}$)[4] | 0.072 (26.6) | 0.077 (32.6) | -- | -- |

Source: PKD_14_129 Report, Table 14.2-1A and Table 14.2-1B; Appendix 16.1.9.1
[1] Ratio of Least Square Means: calculated according to the formula: $e^{(\text{LSM Treatment (B)} - \text{LSM Treatment (A)})} \times 100$
[2] Ln-transformed data
[3] Median values (range)are presented for $T_{max}$
[4] Arithmetic mean values presented

The 40 mg strength of the proposed rosuvastatin capsules meets the BE criteria compared to the 40 mg strength of reference drug under both fasting and fed conditions. The review and acceptance of the clinical studies PKD_14_128 and PKD_14_129 would be conducted and determined by the clinical pharmacology reviewer.

### 4.3 PK linearity of proposed rosuvastatin capsules over the dose range of 5 mg to 80 mg

As Table 11 and Figure 8 show, the PK of rosuvastatin in the proposed capsule formulation has been shown to be linear over the dose range of 5 mg to 80 mg.

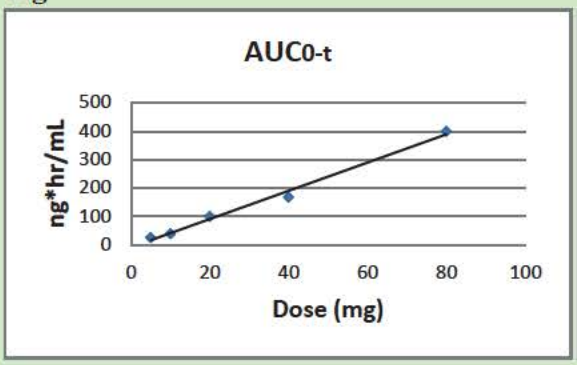
**Table 11. Pooled PK Data Analysis of Dose Proportionality across Clinical Trials in Crestor® (b) (4)**

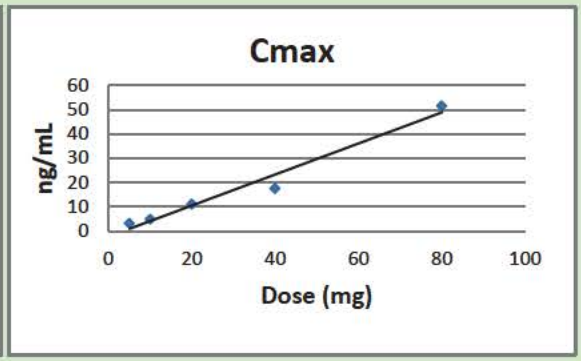
| Parameter (Units) | Geometric Mean (CV %) | | | | |
|---|---|---|---|---|---|
| | 5 mg[a] | 10 mg[b] | 20 mg[c] | 40 mg[d] | 80 mg[e] |
| n | 4 | 34 | 121 | 75 | 176 |
| $C_{max}$ (ng/mL) | 3.12 (42.2) | 4.79 (56.7) | 11.0 (71.8) | 17.5 (69.2) | 51.5 (66.2) |
| $AUC_{0-t}$ (ng•hr/mL) | 25.0 (25.5) | 38.7 (60.7) | 99.4 (62.9) | 167 (56.6) | 399 (53.6) |
| AUC (ng•hr/mL) | NC | NC | 132 (51.7)[1] | 212 (40.1)[2] | 421 (48.9)[3] |
| $T_{max}$ (hr)* | 5.0 | 5.0 | 4.5 | 4.5 | 3.5 |
| $T_{1/2}$ (hr)[4] | NC | NC | 16.4 (25.3[5])[1] | 20.3 (40.2[5])[2] | 17.4 (28.9[5])[3] |

Source: Crestor® (b) (4) Clinical Pharmacology and Biopharmaceutics Review, Table IX
NC=not calculable
*Median value presented
[a]Trial 1
[b]Trials 1, 12, and 47
[c]Trials 1, 2, 3, 19, 47, and 49
[d]Trials 1, 2, 10, 15, 20, and 47
[e]Trials 11, 19, 47, 48, 49, 53, 57, and 58
[1]N=68
[2]N=46
[3]N=147
[4]Samples collected to 96 hours post-dose (LLOQ = unknown).
[5] %CV = (SD/Mean) × 100; calculated independently by SPARC Ltd.

**Figure 8. PK linearity of rosuvastatin capsules over the dose range from 5 mg to 80**

mg




**4.4 Dissolution profiles comparison of different strengths of proposed rosuvastatin capsules**

The Applicant conducted dissolution profiles comparison of different strengths of proposed rosuvastatin capsules 5 mg, 10 mg, 20 mg, and 40 mg in both QC medium pH 6.6 0.05 M citrate buffer as well as multiple pH media including pH 1.2, 4.5, and 6.8.

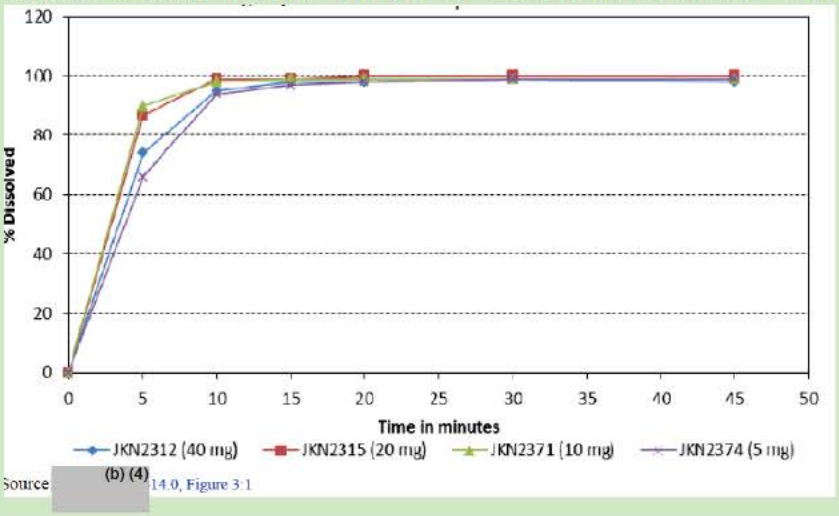
Table 12 and Figure 9 show the comparative dissolution of proposed rosuvastatin capsules 5 mg, 10 mg, 20 mg, and 40 mg in QC medium of pH 6.6 citrate buffer. As Table 12 shows, the drug release already reaches more than (b) (4)% after 10 min in each strength of proposed drug product. The f2 calculations for 5 mg, 10mg, and 20 mg, with 40 mg as the reference were 66.0, 51.2, and 55.0, respectively. Therefore, the dissolution profiles of different strengths of rosuvastatin capsules are similar.

**Table 12. Comparative Dissolution of SPARC Ltd.'s Rosuvastatin Capsules, 5 mg, 10 mg, 20 mg, and 40 mg in pH 6.6 0.05 M Citrate Buffer (QC Medium)**

| Time (min) | Mean Dissolution (%) | | | |
|---|---|---|---|---|
| Strength | 40 mg | 5 mg | 10 mg | 20 mg |
| Batch # | SPARC Ltd. JKN2312 | SPARC Ltd. JKN2374 | SPARC Ltd. JKN2371 | SPARC Ltd. JKN2315 |
| 5 | 74 | 66 | 90 | 87 |
| 10 | 95 | 94 | 98 | 99 |
| 15 | 98 | 97 | 99 | 99 |
| 20 | 98 | 98 | 99 | 100 |
| 30 | 99 | 99 | 99 | 100 |
| 45 | 98 | 99 | 99 | 100 |
| Similarity factor ($f2$) (relative to 40 mg) | | 73 | 59 | 62 |

Source: (b) (4) 14.0, Table 3:2

**Figure 9. Comparative Dissolution of SPARC Ltd.'s Rosuvastatin Capsules, 5 mg, 10 mg, 20 mg, and 40 mg in pH 6.6 0.5 M Citrate Buffer over Time**



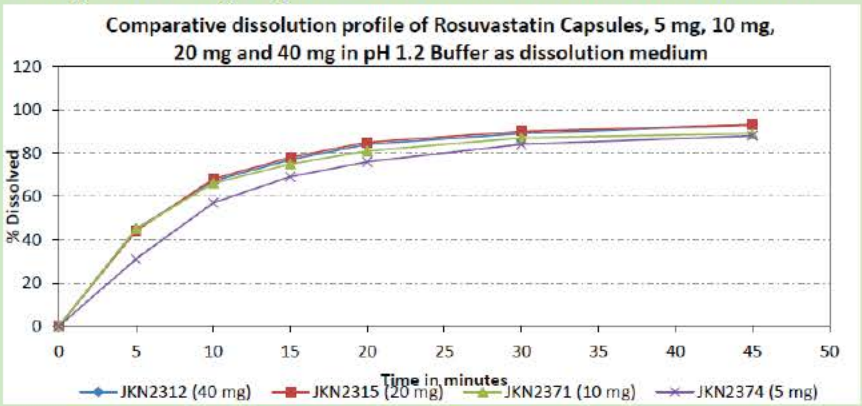

Source (b) (4) 14.0, Figure 3-1

Table 13 and Figure 10 show the comparative dissolution of proposed rosuvastatin capsules 5 mg, 10 mg, 20 mg, and 40 mg in pH 1.2 buffer.

**Table 13. Comparative dissolution profile of Rosuvastatin Capsules, 5 mg, 10 mg, 20 mg and 40 mg in pH 1.2 medium as dissolution medium**

| Time in minutes | JKN2312, 40 mg | JKN2315, 20 mg | JKN2371, 10 mg | JKN2374, 5 mg |
|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 |
| 5 | 45 | 44 | 45 | 31 |
| 10 | 67 | 68 | 66 | 57 |
| 15 | 77 | 78 | 75 | 69 |
| 20 | 84 | 85 | 81 | 76 |
| 30 | 89 | 90 | 87 | 84 |
| 45 | 93 | 93 | 89 | 88 |
| **Similarity factor ($f_2$)** | | **93** | **79** | **52** |

**Figure 10. Comparative dissolution profile of Rosuvastatin Capsules, 5 mg, 10 mg, 20 mg and 40 mg in pH 1.2 Medium as dissolution medium**



Based on f2 calculations and comparative dissolution profiles shown in Figure 10, the dissolution profiles of different strengths of rosuvastatin capsules are similar in pH 1.2 buffer. The reviewer's f2 calculations are slightly different as the f2 values shown in Table 13, which are 92.5, 83.4, and 51.1 (with dissolution of 40 mg strength as the reference). However, the conclusion is consistent.

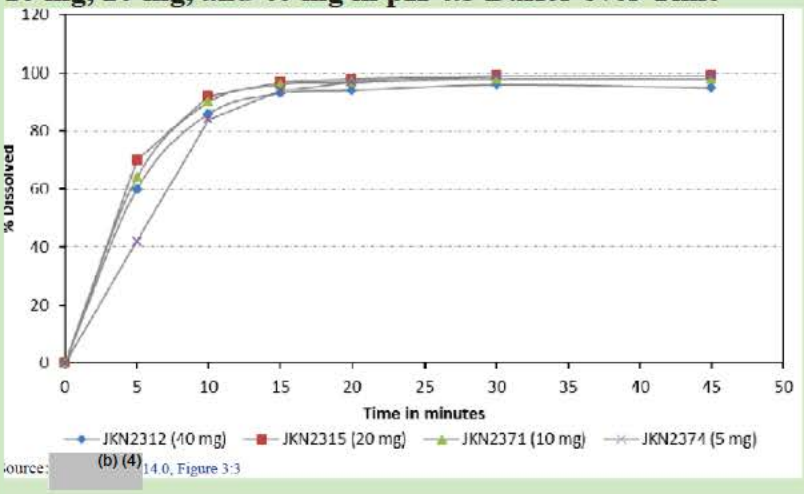
Table 14 and Figure 11 show the comparative dissolution of proposed rosuvastatin capsules 5 mg, 10 mg, 20 mg, and 40 mg in pH 4.5 buffer.

**Table 14. Comparative Dissolution of SPARC Ltd.'s Rosuvastatin Capsules, 5 mg, 10 mg, 20 mg, and 40 mg in pH 4.5 Buffer**

| Time (min) | Mean Dissolution (%) | | | |
|---|---|---|---|---|
| Strength | 40 mg | 5 mg | 10 mg | 20 mg |
| Batch # | SPARC Ltd. JKN2312 | SPARC Ltd. JKN2374 | SPARC Ltd. JKN2371 | SPARC Ltd. JKN2315 |
| 5 | 60 | 42 | 64 | 70 |
| 10 | 86 | 84 | 90 | 92 |
| 15 | 93 | 94 | 96 | 97 |
| 20 | 94 | 97 | 97 | 98 |
| 30 | 96 | 99 | 98 | 99 |
| 45 | 95 | 99 | 98 | 99 |
| Similarity factor (f2) relative to 40 mg | | 55 | 74 | 62 |

Source: (b) (4) 14.0, Table 3:4

**Figure 11. Comparative Dissolution of SPARC Ltd.'s Rosuvastatin Capsules, 5 mg, 10 mg, 20 mg, and 40 mg in pH 4.5 Buffer over Time**




Source: (b) (4) 14.0, Figure 3:3

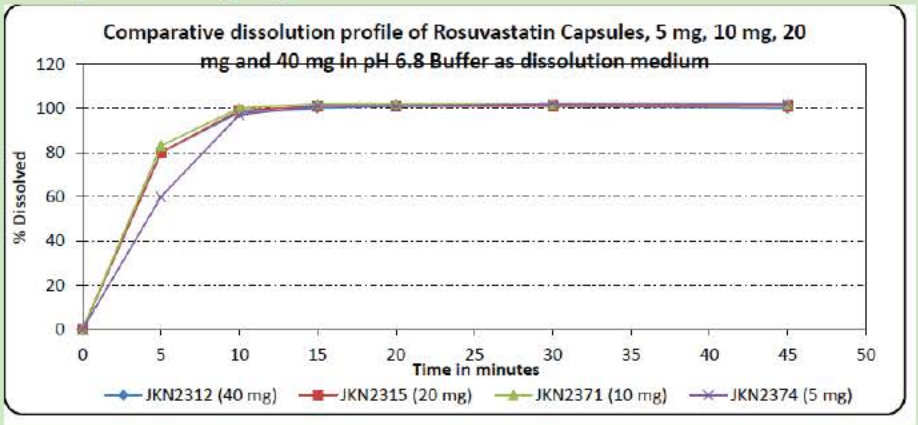
Similarly as the comparative dissolution conducted in QC medium, the drug release in all strength of rosuvastatin capsules reaches more than (b) (4)% within 10 min (the release at 10 min for 5 mg strength is slightly less, which is (b) (4)%). The f2 calculations for 5 mg, 10mg, and 20 mg, with 40 mg as the reference were 51.7, 70.8, and 57.2, respectively. Therefore, the dissolution profiles of different strengths of rosuvastatin capsules are similar.

As evidenced from Table 15 and Figure 12, which show the comparative dissolution of proposed rosuvastatin capsules 5 mg, 10 mg, 20 mg, and 40 mg in pH 6.8 buffer. The f2 calculations for 5 mg, 10mg, and 20 mg, with 40 mg as the reference were 46.8, 79.4, and 94.0, respectively. The dissolution profile of the 5 mg strength is marginally different as that of the 40 mg strength, which is majorly due to the difference at 5 min time point. Since for biowaiver request for immediate release formulation, the dissolution similarity for different strengths is only requested for dissolution conducted in QC medium. Therefore, this difference in pH 6.8 buffer will not be a concern.

**Table 15. Comparative dissolution profile of Rosuvastatin Capsules, 5 mg, 10 mg, 20 mg and 40 mg in pH 6.8 Buffer as dissolution medium**

| Time in minutes | JKN2312, 40 mg | JKN2315, 20 mg | JKN2371, 10 mg | JKN2374, 5 mg |
|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 |
| 5 | 80 | 80 | 83 | 60 |
| 10 | 98 | 99 | 100 | 97 |
| 15 | 100 | 101 | 102 | 101 |
| 20 | 101 | 101 | 102 | 101 |
| 30 | 101 | 101 | 102 | 102 |
| 45 | 100 | 101 | 102 | 102 |
| **Similarity factor ($f_2$)** | | **96** | **83** | **54** |

**Figure12. Comparative dissolution profile of Rosuvastatin Capsules, 5 mg, 10 mg, 20 mg and 40 mg in pH 6.8 Buffer as dissolution medium**




Overall, the compositions of different strengths of rosuvastatin capsules 5 mg, 10 mg, 20 mg, and 40 mg are composition proportional; the dissolution profiles of all strengths of proposed drug product are similar in QC dissolution medium; and the PK of rosuvastatin is linear. Therefore, with bioequivalence of 40 mg strength of proposed drug product with the 40 mg reference drug product, the biowaiver request for the lower strengths 5 mg, 10 mg, and 20 mg are acceptable, pending on the acceptance of BA studies PKD_14_128 and PKD 14 129 by Office of Clinical Pharmacology.

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

**Reviewer's Assessment:**

During the formulation development, various (b) (4) formulations were developed to match the dissolution profiles of the innovator, and met BE with reference drug in the pivotal BE study, and meet stability requirement. The 40 mg of final formulation (to be market formulation) (JKN2312) has been applied in the clinical BA/BE studies PKD_14_128 and PKD_14_129 and compared with the reference drug product. The same batch was also used in the in vitro comparative dissolution study with the reference drug, 40 mg rosuvastatin tablets, as well as other strengths of proposed rosuvastatin capsules 5 mg, 10 mg, and 20 mg. The pivotal /exhibit batches of the proposed drug products have a batch size of (b) (4) kg, which is within (b) (4) fold difference, compared to the batch size of (b) (4) kg in the intended commercial batches. Based on SUPAC-IR, for a batch size difference within (b) (4) fold, regular dissolution test with QC method is sufficient.

As shown in the following table for the dissolution test of one scale up batch (batch size (b) (4) kg) of 40 mg rosuvastatin capsules in QC dissolution method and compared to the reference drug 40 mg rosuvastatin tablet, the dissolution profiles are similar.

| Time (minutes) | JKM5105F | Crestor® 40 mg Tablets (113386) |
|---|---|---|
| | Cumulative Rosuvastatin released (%) | |
| 10 | 93 | 88 |
| 20 | 97 | 93 |
| 30 | 98 | 95 |
| 45 | 98 | 97 |

Therefore, there is no concern on formulation bridging.

## OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS

**Reviewer's Assessment and Signature:**

**1. The dissolution method and the dissolution acceptance criterion of Q= (b) (4) % in 20 min are acceptable.**

| | |
|---|---|
| **Dissolution Medium** | pH 6.6, 0.05M sodium citrate buffer |
| **Volume** | 900 mL |
| **Apparatus** | USP Apparatus II (Paddle) |
| **Speed** | 50 rpm |
| **Sampling Times** | 5, 10, 15, 20, 30, 45 minutes |
| **Proposed specification** | Not less than (b)(4)% (Q) of label claim in 20 minutes.<br>For release at S1, no individual unit is less than (b)(4)% of label claim in 20 minutes.<br>For release at S2, average of 12 units is equal to or greater than (b)(4)% of label claim and no individual unit is less than (b)(4)% of label claim in 20 minutes.<br>For release at S3, average of 24 units is equal to or greater than (b)(4)% of label claim and not more than 2 units are less than (b)(4)% of label claim and no unit is less than (b)(4)% of label claim in 20 minutes. |
| **Detection** | HPLC, at nm |

Source: (b) (4) 8.2, Specification 0012570 Rev. 9.0

**2. The biowaiver request for the lower strengths 5 mg, 10 mg, and 20 mg are acceptable, pending on the acceptance of BA/BE studies conducted with the higher strength 40 mg by Office of Clinical Pharmacology.**

**3. The results of in-use-study of rosuvastatin (b) (4) on applesauce are acceptable, and the time of 60 min is suitable for the consumption of rosuvastatin (b) (4) /applesauce mixture after sprinkling (b) (4) onto applesauce.**

**4. The in vitro NG tube dissolution study was acceptable. The intact rosuvastatin capsules and rosuvastatin (b) (4) dispersion showed comparable dissolution for all storage periods up to 90 min. Rosuvastatin could be completely recovered while dispersing capsule (b) (4) into 40 mL water and passing through (b) (4) NG tube.**

**Vincent (Peng) Duan, Ph.D.**

**04/28/2016**

**<u>Secondary Review Comments and Concurrence</u>:**

**I concur. 05/13/16**

**Tien-Mien Chen, Ph.D.**

**Acting Biopharmaceutics Lead**
**Biopharmaceutics Branch II/DB/ONDP/OPQ**

Attachment

| From Initial Risk Identification | | | Review Assessment | | |
|---|---|---|---|---|---|
| **Attribute/ CQA** | **Factors that can impact the CQA** | **Initial Risk Ranking** | **Risk Mitigation Approach** (b) (4) | **Final Risk Evaluation** | **Lifecycle Considerations/ Comments** |
| Drug content/Assay | Formulation<br>Process<br>Container closure | H | | L | none |
| Impurities/ degradants | Formulation<br>Process<br>Container closure | H | | L | none |
| Appearance | Formulation<br>Process<br>Container closure | H | | L | none |
| Drug release rate | Formulation<br>Process | H | | L | reference the pharmaceutical development for any change in formulation or process |
| Content uniformity | Process | H | | L | evaluate any change in the specific process steps |

# OVERALL ASSESSMENT AND SIGNATURE:

**Application Technical Lead Signature:**

**I concur with the reviewers' conclusions; see the Executive Summary.**

Suong T. Tran -S

Digitally signed by Suong T Tran S
DN: c=US, o=U S Government, ou=HHS, ou=FDA, ou=People, cn=Suong T Tran S, 0.9.2342.19200300.100.1.1=1300101829
Date: 2016.05.18 14:49:27 04'00'

**Suong (Su) Tran, PhD**

[See digital signature and date in the Executive Summary]