# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 209875Orig1s000

# PRODUCT QUALITY REVIEW(S)

**Recommendation:**
**APPROVAL**
**(including the Facility Review/Overall Manufacturing Inspection Recommendation)**

# NDA 209875
# Review #1
# Review Date (see last page)

| | |
|---|---|
| **Drug Name/Dosage Form** | pitavastatin tablet |
| **Strength** | 1 mg, 2 mg, and 4 mg (pitavastatin) |
| **Route of Administration** | oral |
| **Rx/OTC Dispensed** | Rx |
| **Applicant** | Lupin |

| SUBMISSION(S) REVIEWED | DOCUMENT DATE |
|---|---|
| 0000 | 10/21/16 |
| 0009 | 5/2/17 |
| 0010 | 6/21/17 |

**Quality Review Team**

| DISCIPLINE | REVIEWER | DIVISION/OFFICE |
|---|---|---|
| Regulatory Business Process Manager | Anika Lalmansingh | Regulatory Business Process Management I/OPRO |
| Application Technical Lead | Suong (Su) Tran | New Drug Products II/ONDP |
| API | Xavier Ysern/Donna Christner | New Drug API/ONDP |
| Drug Product | Elise Luong/Danae Christodoulou | New Drug Products II/ONDP |
| Process | Ted Chang/Yong Hu | Process Assessment II/OPF |
| Facility | Sherry Shen/Vidya Pai | Inspectional Assessment/OPF |
| Biopharmaceutics | Hansong Chen/Albert Chen | Biopharmaceutics/ONDP |

## Quality Review Data Sheet

1. **RELATED/SUPPORTING DOCUMENTS:**
   A. **DMFs:** Adequate
   B. **Other Documents:** not applicable
2. **CONSULTS:** not applicable

# Executive Summary

## I. Recommendation and Conclusion on Approvability

The final OPQ recommendation is for Approval, including the overall manufacturing inspection recommendation.

## II. Summary of Quality Assessment

### A. Product Overview

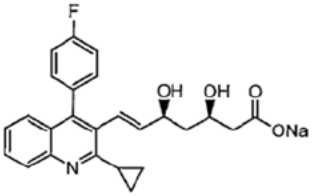
NDA 209875 is a 505(b)(2) application for pitavastatin sodium, relying on FDA's findings of safety and effectiveness for the listed LIVALO (pitavastin calcium). The two NDAs have different applicants with no right of reference. Both products have the same dosage form (immediate release oral tablet) and strengths: 1 mg, 2 mg, and 4 mg pitavastatin (free-acid).

BE studies LBC-ARL/16/056 and LBC-ARL/16/057 were conducted with the highest strength, 4 mg, of LIVALO and the new product. The 4 mg batch M590478 of the new product used in the BE studies has the commercial formulation and was manufactured at the commercial drug product facility at pilot-scale ( (b) (4) kg). The biowaiver request for the lower strengths, 1 mg and 2 mg, is granted based on the proportional composition of all three strengths and their adequately similar dissolution profiles.

| | |
|---|---|
| **Proposed Indication(s)** | Patients with primary hyperlipidemia or mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol, low-density lipoprotein cholesterol, apolipoprotein B, triglycerides, and to increase high-density lipoprotein cholesterol. |
| **Duration of Treatment** | chronic |
| **Maximum Daily Dose** | 4 mg |
| **Alternative Methods of Administration** | n/a |

### B. Quality Assessment Overview

**Drug Substance**




The drug substance is pitavastatin sodium.

DMF (b) (4) is referenced for all CMC information on the API and is currently adequate.
Polymorph forms and particle size distribution of the API are not critical attributes in the manufacture of the drug product because the API is BCS I/III and is dissolved during the drug product manufacture.

**Drug Product**
The drug product is an immediate release oral tablet. Dosage strengths are 1 mg, 2 mg, and 4 mg pitavastatin, which are equivalent to 1.052 mg, 2.103 mg, and 4.206 mg pitavastatin sodium, respectively. The three strengths are identified by different colors and debossing. The strengths differ by the amount of formulated blend per capsule.

Excipients: hypromellose, lactose monohydrate, low substituted hydroxypropylcellulose, magnesium stearate (b) (4) and sodium bicarbonate. The film coating contains: colloidal anhydrous silica, hypromellose, titanium dioxide and triethyl citrate. There is no novel excipient..

The product manufacturing process consists (b) (4)

The regulatory drug product specification is adequate based on the supporting release and stability data and ICH guidelines for this type of dosage form. Limits on degradants meet the applicable ICH identification and qualification threshold for the maximum daily dose of 4 mg. They are the same as impurities listed in the drug substance specification (with the exception of (b) (4) (b) (4) which are process impurities specific to the drug substance and are not included in the drug product specification). Degradants (b) (4) have structural alerts but were found by Ames testing to be negative for genotoxicity (see the separate review by the Pharmacology Toxicology team).

Primary container closure system: HDPE bottles with child-resistant closures and desiccant packs. Adequate information on the drug-contact components is included in the NDA.

Expiration Date & Storage Conditions: 24 months at room temperature (excursions permitted to 15-30 C), protected from light.

Stability data include three primary stability batches of each strength, manufactured at the commercial facility and scale (b) (4) by the commercial process, with the commercial formulation, and packaged in all commercial bottle configurations. The NDA includes data from 12 months at 25 °C/60% RH and 6 months at 40 °C/75% RH.

**C. Special Product Quality Labeling Recommendation**: not applicable

**D. Life Cycle Knowledge Information/ Final Risk Assessment:**

| | |
|---|---|
| API | none |
| Drug product | page 62 of Chapter II |
| Process | none |
| Facilities | page 4 of Chapter VI |
| Biopharmaceutics | none |

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

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: 2017.07.18 09:24:16 -04'00'

**Suong (Su) Tran, Ph.D.**
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# CHAPTERS: Primary Quality Assessment

Chapter I: Drug Substance
Chaper II: Drug Product
Chapter III: Environmental Assessment
Chapter IV: Labeling
Chapter V: Process
Chapter VI: Facilities
Chapter VII: Biopharmaceutics
Chapter VIII: Microbiology
Attachment I: Final Risk Assessment (see last page of Executive Summary)

# CHAPTER I: Drug Substance

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Xavier Ysern

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Donna Christner

Digitally signed by Donna Christner
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# CHAPTER II: Drug Product

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# CHAPTER III: Environmental Analysis

see chapter II

# CHAPTER IV: Labeling

see chapter II

# CHAPTER V: Process

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# CHAPTER VII: Biopharmaceutics

# BIOPHARMACEUTICS

**Product Background:**

**NDA/ANDA:** NDA 209875

**Drug Product Name / Strength:** Pitavastatin Tablets, 1 mg, 2 mg, and 4 mg

**Route of Administration:** Oral

**Applicant Name:** Lupin Limited

***Review Summary:***

The Listed Drug LIVALO® (pitavastatin calcium) immediate-release tablets, 1 mg, 2 mg, and 4 mg, developed by Kowa Co Ltd, was approved by the FDA under NDA 022363 on 08/03/2009 for prescription use. It is indicated for treatment of primary hyperlipidemia and mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated TC, LDL-C, Apo B, and TG and to increase HDL-C.

Using LIVALO® (pitavastatin calcium) tablets, 1 mg, 2 mg, and 4 mg as the Listed Drug, Lupin Limited developed Pitavastatin Sodium immediate-release tablets, 1 mg, 2 mg, and 4 mg and submitted the application under NDA 209875 seeking approval through a 505 (b) (2) regulatory pathway. The proposed pitavastatin sodium tablets, 1, 2, and 4 mg (b) (4) .

The Biopharmaceutics review focuses on the dissolution method development, dissolution data, dissolution specification, and biowaiver request for NDA 209875.

The Applicant adopted the dissolution method listed in the FDA dissolution database for pitavastatin calcium to conduct dissolution tests, which is acceptable. The following dissolution specification has been set as agreed upon with the Applicant:

**NLT (b) (4) % (Q) at 20minutes**

The Applicant provided sufficient dissolution data to support the biowaiver of in vivo BA/BE studies for two lower strengths, 2 mg and 1 mg. The waiver is therefore granted.

From the Biopharmaceutics perspective, NDA 209875 for Pitavastatin Tablets, 1 mg, 2 mg, and 4 mg is reviewed and found ADEQUATE for approval.

**List Submissions being reviewed (table):**

Application 209875 - Sequence 0000 - 0000 (1) 10/21/2016 ORIG-1 /Multiple Categories/Subcategories
Application 209875 - Sequence 0009 - 0009 (10) 05/02/2017 ORIG-1 /Quality/Response To Information Request

| Module | Content |
|---|---|
| 1.12.15 | Request for Waiver of in vivo Bioavailability Studies |
| 2..3.P | Quality overall summary- Drug product |
| 2.7.1 | Summary of Biopharmaceutic Studies and Associated Analytical Methods (in vitro dissolution data) |
| 3.2.P.1 | Description and composition of the drug product |
| 3.2.P.2.2 | Pharmaceutical Development-Drug product |
| 3.2.P.5.1 | Specifications |
| 3.2.P.5.2 | Analytical Procedures |
| 3.2.P.5.2 | Validation of Analytical Procedures |
| 3.2.P.5.6 | Justification of specifications |

**Highlight Key Outstanding Issues from Last Cycle:** None

**Concise Description Outstanding Issues Remaining:**

***BCS Designation***

**Reviewer's Assessment:** The Applicant did not report Pitavastatin sodium's BCS classification. However, Pitavastatin sodium has high solubility across the physiological pH range, and it can be considered as Class I/III drug.

**Solubility:**

Pitavastatin sodium exists in [redacted] (b) (4)

[redacted] Drug substance manufacturer consistently produces [redacted] (b) (4) of the drug substance for drug product development. [redacted] (b) (4) is considered as highly soluble per BCS criteria.

Pitavastatin sodium is freely soluble in water and shows pH dependent solubility. It can be considered as highly soluble drug substance as per BCS, as volume of media required to dissolve highest dose strength (4 mg) is less than 0.3 mL in the pH range 1.2 to pH 7.5.

Table 1. Solubility of Pitavastatin Sodium (Batch No.: 410/NDM/C-491/073) in different pH aqueous solution at 37°C

| Media | Solubility (mg/mL) | pH before saturation | pH after saturation | Volume of Media Required to Dissolve Highest Dose strength (4 mg) |
|---|---|---|---|---|
| 0.1 N Hydrochloric acid (pH 1.2) | 19.098 | 1.17 | 2.34 | 0.21 mL |
| pH 4.5 Acetate Buffer | 228.321 | 4.53 | 7.05 | 0.02 mL |
| Water | 226.316 | 6.59 | 9.07 | 0.02 mL |
| pH 6.8 Phosphate Buffer | 188.460 | 6.81 | 7.31 | 0.02 mL |
| pH 7.5 Phosphate Buffer | 148.648 | 7.53 | 7.79 | 0.03 mL |

**Permeability: Not reported.**

**Dissolution: See the Biopharm review below**

***Dissolution Method and Acceptance Criteria***

**Reviewer's Assessment:**

**I. Dissolution method**

The Applicant used the FDA recommended dissolution method to conduct dissolution tests.

Table 2. The dissolution method used by the Applicant

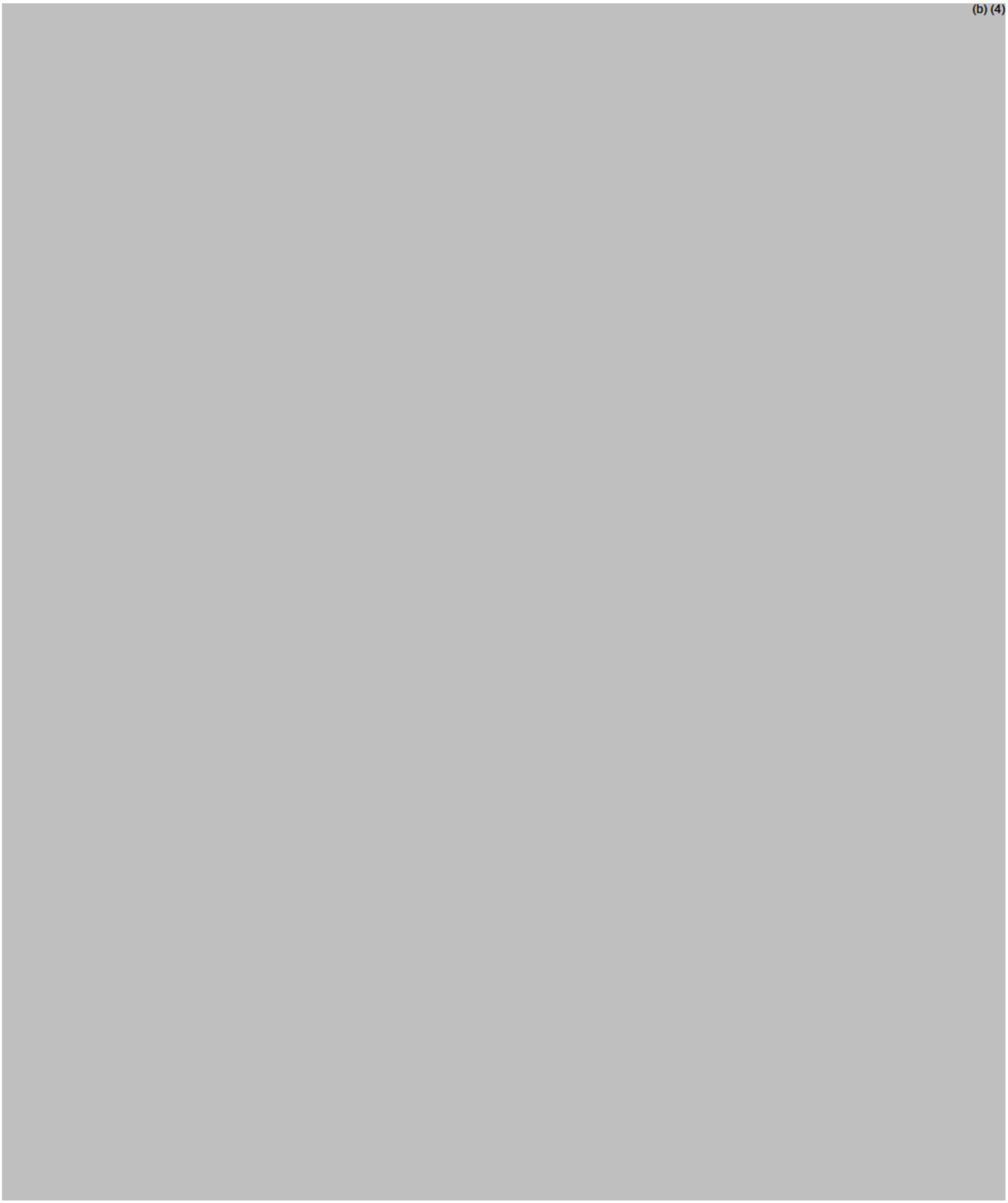
| | NDA 209875 | FDA database method for **pitavastatin calcium** |
|---|---|---|
| Apparatus | USP apparatus –I (basket) | USP apparatus –I (basket) |
| Speed | 35 rpm | 35 rpm |
| Dissolution media | 0.05 M pH 6.8 phosphate buffer ( Deaerated) | 0.05 M pH 6.8 phosphate buffer ( Deaerated) |
| Volume | 900 mL | 900 mL |
| Time (min) | 5, 10, 15, 20, 30, and 45 | 5, 10, 15, 20, 30, and 45 |
| Temperature | 37 ± 0.5 °C | 37 ± 0.5 °C |
| Specifications | The Applicant's proposed specification: NLT (b) (4) % (Q) in (b) (4) minutes | LD specification: NLT (b) (4) % (Q) in (b) (4) minutes |

## II. Dissolution Method Development for Pitavastatin Oral Tablets, 1, 2, and 4 mg

Although the Applicant adopted the FDA database method for their proposed product, they still conducted the dissolution method development.

(b) (4)

(b) (4)



(b) (4)

[redacted]

## III. Analytical Method for Dissolution

The Applicant used HPLC with UV detection to determine the concentrations of the dissolution samples. The UV detection wavelength was set at 244 nm. The percentage of drug release is calculated using the following equations:

$$\% \text{ Drug release} = \frac{A_{Spl}}{A_{Std}} \times \frac{W_{Std}}{D_{Std}} \times \frac{D_{Spl}}{L.C} \times \frac{P}{100} \times \frac{421.46}{443.15} \times 100 + D$$

Correction factor = V x R / MV

Where:

Aspl = Area of Pitavastatin peak in Sample chromatogram

Astd = Average area of Pitavastatin peak in standard chromatogram

Wstd = Weight of Pitavastatin Sodium In-House working standard in mg.

Dstd = Dilution of standard preparation.

MV = Volume of dissolution media.

Dspl = Dilution of sample preparation.

P = Potency of Pitavastatin Sodium In-House working standard (as is basis)

LC = Label Claim of Pitavastatin (mg/tablet)

D = Sum of correction factors for all previous time points

The Applicant use the following HPLC parameters for its analytical method for dissolution

| Parameter | |
|---|---|
| Column | lnertsil ODS 3V, 150 x 4.6 mm, 5µ |
| Flow rate | 1.2 mL/ min |
| Detector | 244 nm |
| Injection volume | 100 µL |
| Runtime | 6 minutes |
| Column temperature | 30°C |
| Mobile phase | Buffer and Acetonitrile in the ratio (650:350)<br>Buffer: 0.3 mL orthophosphoric acid to 1000 mL of water |

## IV. Validation of Analytical procedures for Dissolution

The analytical method for dissolution was validated in Lupin Limited, India. The validation includes specificity, linearity & range, accuracy, precision (repeatability and intermediate precision), stability in analytical solution, effect of filter variation, and robustness.

## V. Dissolution data and specification

The Applicant provided the complete dissolution for the following batches of test product and LD (Table 5). The data are listed in Appendixes for details. The Applicant used fresh lot of test product and unexpired lot of reference product for in vitro dissolution tests, which meets the Agency's expectation. Test Product Batch M590440 and RLD Batch 3121762 were used for the bioequivalence studies.

Table 5. Batch information of test products and RLD

| Strength | Batch number | Manufacturing date or | Purpose |
|---|---|---|---|

| | | Expiration date | |
|---|---|---|---|
| 4 mg | M590440 | Sep 2015 | Biobatch |
| | M590446 | Sep 2015 | Stability |
| | M590455 | Sep 2015 | Stability |
| | 3121762 | April 2017 | LD |
| 2 mg | M590436 | Sep 2015 | stability |
| | M590445 | Sep 2015 | stability |
| | M590465 | Sep 2015 | Stability |
| | 3130302 | Dec 2017 | LD |
| 1 mg | M590435 | Sep 2015 | stability |
| | M590444 | Sep 2015 | stability |
| | M590464 | Sep 2015 | Stability |
| | 3130787 | Oct 2017 | LD |

Table 6. Mean dissolution data comparison between the test products and RLDs

| Batch/Time points(min) | 5 | 10 | 15 | 20 | 30 | 45 |
|---|---|---|---|---|---|---|
| Test Product 4 mg Batch M590440 | 7 | 52 | 90 | 97 | 100 | 100 |
| Test Product 4 mg Batch M590446 | 7 | 53 | 90 | 97 | 100 | 101 |
| Test Product 4 mg Batch M590455 | 8 | 48 | 84 | 94 | 99 | 100 |
| RLD 4 mg Batch 3121762 | 37 | 55 | 65 | 73 | 85 | 95 |
| Test Product 2 mg Batch M590436 | 18 | 72 | 98 | 100 | 100 | 101 |
| Test Product 2 mg Batch M590445 | 17 | 71 | 97 | 100 | 101 | 101 |
| Test Product 2 mg Batch M590465 | 29 | 73 | 95 | 98 | 98 | 98 |
| RLD 2 mg Batch 3130302 | 54 | 69 | 79 | 86 | 94 | 98 |
| Test Product 1 mg Batch M590435 | 49 | 99 | 100 | 101 | 101 | 101 |
| Test Product 1 mg Batch M590444 | 44 | 97 | 99 | 99 | 99 | 99 |
| Test Product 1 mg Batch M590464 | 56 | 98 | 100 | 100 | 101 | 101 |
| RLD 1 mg Batch 3130787 | 67 | 83 | 93 | 97 | 101 | 102 |

The Applicant proposed the following specifications for its drug product:

- Not less than (b)(4)% (Q) of the labeled amount dissolved in (b)(4) minutes

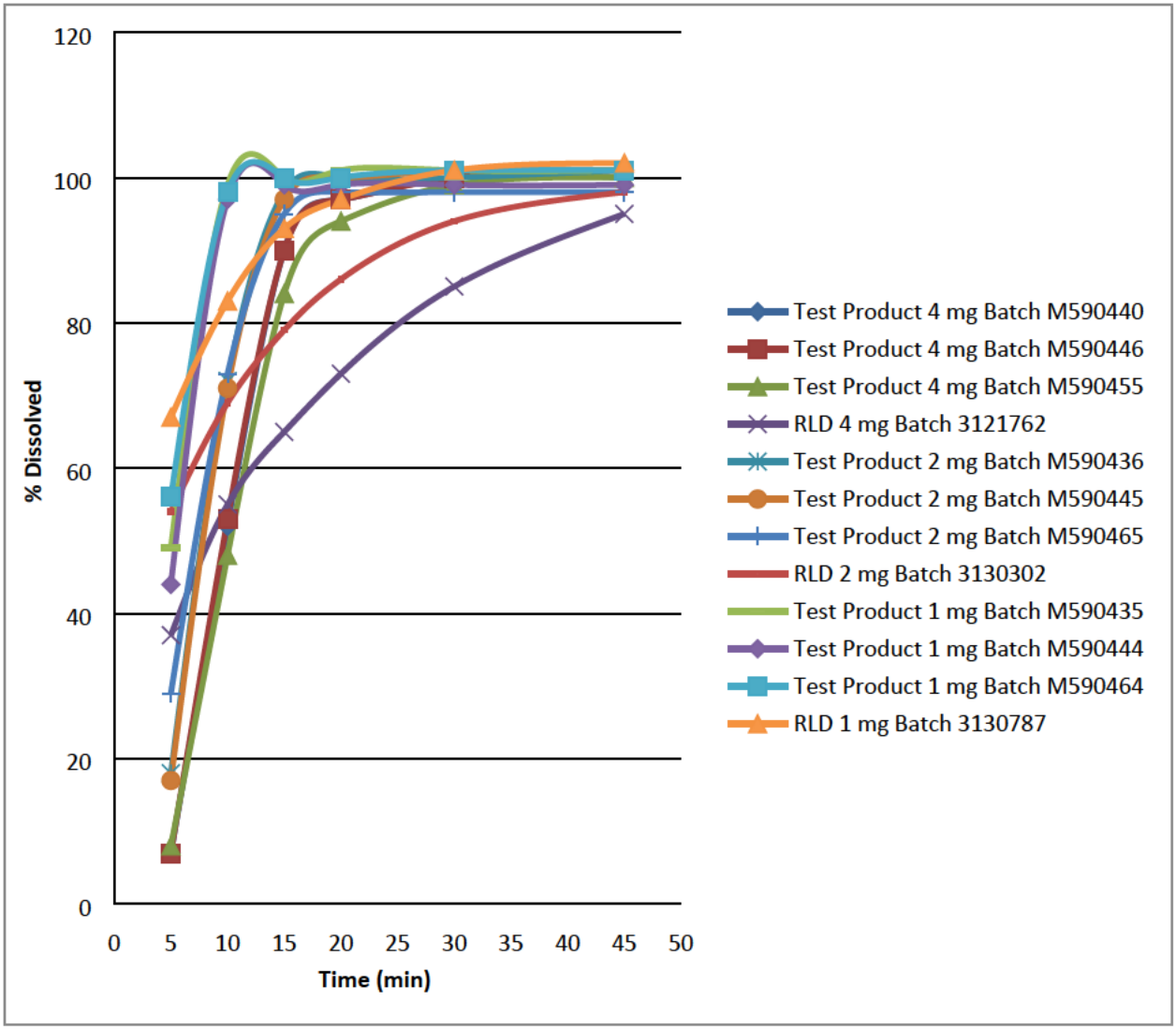
The data in Table 6 show that all batches of test product have a mean dissolution of ≥(b)(4)% at 20 minutes. Therefore, the Applicant's proposed specification (NLT (b)(4)% (Q) of the label claim in (b)(4) minutes) is liberal.

Based on the data, this Reviewer recommended the following dissolution specification:

- Not less than (b) (4)% (Q) of the labeled amount dissolved in 20 minutes

The applicant was asked to acknowledge the acceptance of the FDA-recommended specification and updated relevant parts of this NDA accordingly in the Biopharmaceutics Information Request (IR), which was included in the next section.

Figure 2. Mean dissolution profile comparison between the Test products and RLD in pH 6.8 phosphate buffer




## VI. Information Request (IR) and response

One item Biopharmaceutics IR was sent to the Applicant on 4/3/2017. On 5/2/2016, the Applicant responded to the IR. The following are the Biopharmaceutics IR, the Applicant's response, and this Reviewer's assessment of the Applicant's response.

**IR**

Based on the data provided, the proposed dissolution acceptance criterion is too wide, and therefore, it is not acceptable. Revise the dissolution acceptance criterion as follows:

NLT (b)(4)% (Q) at 20 minutes

We request that you acknowledge your acceptance of our revised dissolution acceptance criterion above for quality control purpose on release and stability testing of your drug product and update the drug product specification section under Module 3.2 .P. 5 .1. and other related sections in your NDA submission accordingly.

**The Applicant's response**

The Applicant stated that they accept the FDA recommended dissolution specification for their proposed product and updated the drug product specification section under Module 3.2 .P. 5 .1. and other related sections in their NDA submission accordingly.

**Reviewer's assessment**

*The response is adequate.*

**Appendix I the complete dissolution data in pH 6.8 phosphate buffer**

**4 mg**

| Product | Batch No. | Time in Min. | % Drug Released for Pitavastatin | | | | | | | | | | | | Mean | Min. | Max. | % RSD | Date of Analysis |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | | | | | |
| Pitavastatin Tablets, 4 mg [Test Product] | M590440 | 5 | | | | | | | | | | | | (b) (4) | 7 | 2 | 11 | 45.09 | 06-May-16 |
| | | 10 | | | | | | | | | | | | | 52 | 46 | 56 | 5.89 | |
| | | 15 | | | | | | | | | | | | | 90 | 81 | 99 | 6.87 | |
| | | 20 | | | | | | | | | | | | | 97 | 94 | 101 | 3.02 | |
| | | 30 | | | | | | | | | | | | | 100 | 98 | 101 | 1.12 | |
| | | 45 | | | | | | | | | | | | | 100 | 98 | 102 | 0.98 | |
| Pitavastatin Tablets, 4 mg [Test Product] | M590446 | 5 | | | | | | | | | | | | | 7 | 1 | 26 | 100.31 | 06-May-16 |
| | | 10 | | | | | | | | | | | | | 53 | 38 | 72 | 21.67 | |
| | | 15 | | | | | | | | | | | | | 90 | 72 | 100 | 9.77 | |
| | | 20 | | | | | | | | | | | | | 97 | 88 | 101 | 4.48 | |
| | | 30 | | | | | | | | | | | | | 100 | 97 | 101 | 1.24 | |
| | | 45 | | | | | | | | | | | | | 101 | 100 | 102 | 0.65 | |
| Pitavastatin Tablets, 4 mg [Test Product] | M590455 | 5 | | | | | | | | | | | | | 8 | 2 | 20 | 59.85 | 06-May-16 |
| | | 10 | | | | | | | | | | | | | 48 | 33 | 56 | 16.40 | |
| | | 15 | | | | | | | | | | | | | 84 | 67 | 98 | 10.81 | |
| | | 20 | | | | | | | | | | | | | 94 | 82 | 101 | 5.87 | |
| | | 30 | | | | | | | | | | | | | 99 | 96 | 101 | 1.43 | |
| | | 45 | | | | | | | | | | | | | 100 | 98 | 102 | 1.08 | |
| LIVALO® (pitavastatin) tablets, 4 mg [Reference Product] | 3121762 | 5 | | | | | | | | | | | | | 37 | 27 | 47 | 20.03 | 28-Oct-15 |
| | | 10 | | | | | | | | | | | | | 55 | 40 | 68 | 14.25 | |
| | | 15 | | | | | | | | | | | | | 65 | 50 | 78 | 12.01 | |
| | | 20 | | | | | | | | | | | | | 73 | 59 | 88 | 10.12 | |
| | | 30 | | | | | | | | | | | | | 85 | 75 | 95 | 7.09 | |
| | | 45 | | | | | | | | | | | | | 95 | 89 | 102 | 4.39 | |

## 2 mg

| Product | Batch No. | Time in Min. | % Drug Released for Pitavastatin | | | | | | | | | | | | Mean | Min. | Max. | % RSD | Date of Analysis |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | | | | | |
| Pitavastatin Tablets, 2 mg [Test Product] | M590436 | 5 | | | | | | | | | | | | (b) (4) | 18 | 6 | 24 | 27.05 | 05-May-16 |
| | | 10 | | | | | | | | | | | | | 72 | 59 | 83 | 11.35 | |
| | | 15 | | | | | | | | | | | | | 98 | 90 | 101 | 3.77 | |
| | | 20 | | | | | | | | | | | | | 100 | 98 | 101 | 1.08 | |
| | | 30 | | | | | | | | | | | | | 100 | 98 | 103 | 1.23 | |
| | | 45 | | | | | | | | | | | | | 101 | 98 | 103 | 1.43 | |
| Pitavastatin Tablets, 2 mg [Test Product] | M590445 | 5 | | | | | | | | | | | | | 17 | 6 | 33 | 46.81 | 05-May-16 |
| | | 10 | | | | | | | | | | | | | 71 | 55 | 82 | 13.49 | |
| | | 15 | | | | | | | | | | | | | 97 | 89 | 104 | 4.73 | |
| | | 20 | | | | | | | | | | | | | 100 | 97 | 103 | 2.00 | |
| | | 30 | | | | | | | | | | | | | 101 | 99 | 103 | 1.43 | |
| | | 45 | | | | | | | | | | | | | 101 | 99 | 104 | 1.50 | |
| Pitavastatin Tablets, 2 mg [Test Product] | M590465 | 5 | | | | | | | | | | | | | 29 | 25 | 36 | 12.89 | 05-May-16 |
| | | 10 | | | | | | | | | | | | | 73 | 60 | 84 | 9.23 | |
| | | 15 | | | | | | | | | | | | | 95 | 89 | 100 | 4.34 | |
| | | 20 | | | | | | | | | | | | | 98 | 94 | 100 | 1.97 | |
| | | 30 | | | | | | | | | | | | | 98 | 95 | 100 | 1.53 | |
| | | 45 | | | | | | | | | | | | | 98 | 95 | 100 | 1.44 | |
| LIVALO® (pitavastatin) tablets, 2 mg [Reference Product] | 3130302 | 5 | | | | | | | | | | | | | 54 | 38 | 76 | 17.62 | 11-Dec-15 |
| | | 10 | | | | | | | | | | | | | 69 | 57 | 87 | 11.57 | |
| | | 15 | | | | | | | | | | | | | 79 | 68 | 95 | 9.36 | |
| | | 20 | | | | | | | | | | | | | 86 | 78 | 97 | 6.35 | |
| | | 30 | | | | | | | | | | | | | 94 | 89 | 99 | 2.87 | |
| | | 45 | | | | | | | | | | | | | 98 | 96 | 100 | 1.20 | |

## 1 mg

| Product | Batch No. | Time in Min. | % Drug Released for Pitavastatin | | | | | | | | | | | | Mean | Min. | Max. | % RSD | Date of Analysis |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | | | | | |
| Pitavastatin Tablets, 1 mg [Test Product] | M590435 | 5 | (b) (4) | | | | | | | | | | | | 49 | 40 | 63 | 14.03 | 03-May-16 |
| | | 10 | | | | | | | | | | | | | 99 | 90 | 103 | 3.90 | |
| | | 15 | | | | | | | | | | | | | 100 | 97 | 104 | 2.18 | |
| | | 20 | | | | | | | | | | | | | 101 | 98 | 105 | 2.24 | |
| | | 30 | | | | | | | | | | | | | 101 | 97 | 104 | 2.04 | |
| | | 45 | | | | | | | | | | | | | 101 | 97 | 104 | 2.05 | |
| Pitavastatin Tablets, 1 mg [Test Product] | M590444 | 5 | | | | | | | | | | | | | 44 | 29 | 64 | 22.01 | 07-May-16 |
| | | 10 | | | | | | | | | | | | | 97 | 88 | 101 | 4.80 | |
| | | 15 | | | | | | | | | | | | | 99 | 94 | 102 | 2.26 | |
| | | 20 | | | | | | | | | | | | | 99 | 94 | 102 | 2.28 | |
| | | 30 | | | | | | | | | | | | | 99 | 93 | 102 | 2.42 | |
| | | 45 | | | | | | | | | | | | | 99 | 95 | 102 | 2.19 | |
| Pitavastatin Tablets, 1 mg [Test Product] | M590464 | 5 | | | | | | | | | | | | | 56 | 44 | 68 | 14.11 | 03-May-16 |
| | | 10 | | | | | | | | | | | | | 98 | 92 | 102 | 3.97 | |
| | | 15 | | | | | | | | | | | | | 100 | 96 | 102 | 1.75 | |
| | | 20 | | | | | | | | | | | | | 100 | 97 | 103 | 1.77 | |
| | | 30 | | | | | | | | | | | | | 101 | 97 | 103 | 1.81 | |
| | | 45 | | | | | | | | | | | | | 101 | 97 | 103 | 1.62 | |
| LIVALO® (pitavastatin) tablets, 1 mg [Reference Product] | 3130787 | 5 | | | | | | | | | | | | | 67 | 55 | 90 | 16.75 | 23-Nov-15 |
| | | 10 | | | | | | | | | | | | | 83 | 75 | 94 | 8.96 | |
| | | 15 | | | | | | | | | | | | | 93 | 83 | 103 | 8.64 | |
| | | 20 | | | | | | | | | | | | | 97 | 89 | 102 | 4.66 | |
| | | 30 | | | | | | | | | | | | | 101 | 98 | 104 | 1.58 | |
| | | 45 | | | | | | | | | | | | | 102 | 99 | 103 | 1.15 | |

***Clinical relevance of dissolution method & acceptance criteria (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)***

**Reviewer's Assessment:** N/A

***Application of dissolution/IVIVC in QbD***

(b) (4)



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(b) (4)

***Bridging of Formulations***

**Reviewer's Assessment:**

The formulation used for the pivotal studies is the same as the commercial one, and the scale-up batch size of the commercial batches is not more than 10 times that of the exhibit batches. Therefore, the bridging of formulation is not needed.

***Biowaiver Request***

**Reviewer's Assessment:**

The Applicant conducted two bioequivalence studies (under fasting and fed conditions) to compare the highest strength of test product, 4 mg (Lot No.: M590440) with the Listed Drug-LIVALO® (pitavastatin calcium) 4 mg (Lot No.: 3121762). The study results are pending on Clinpharm Review conclusion (for additional details, please refer to clinical pharmacology review). The Applicant requested the biowaiver for the two lower strengths 2 mg and 1 mg.

## A. Formulation of the test products

Table 8. Qualitative and Quantitative Composition of the Drug Products

| Ingredients | 1 mg Quantity mg/tablet | 2 mg Quantity mg/tablet | 4 mg Quantity mg/tablet | % w/w | Category | Reference to Standards |
|---|---|---|---|---|---|---|
| **CORE COMPOSITION** | | | | | | |
| [redacted] | | | | | | (b) (4) |
| Pitavastatin sodium* (Equivalent to Pitavastatin) | | | | | (b) (4) | IH |
| Lactose monohydrate** (b) (4) | | | | | | NF |
| Low Substituted Hydroxypropyl Cellulose (b) (4) | | | | | | NF |
| Hypromellose (b) (4) (b) (4) | | | | | | USP |
| Sodium bicarbonate (b) (4) (b) (4) | | | | | | USP |
| (b) (4) (b) (4) | | | | | | USP |
| | | | | | | USP |
| Low Substituted Hydroxypropyl Cellulose (b) (4) | | | | | | NF |
| Magnesium Stearate (b) (4) | | | | | | NF |
| [redacted] | | | | | (b) (4) | -- |
| [redacted] | | | | | | IH |
| [redacted] | | | | | | USP |
| **Total Weight of Coated Tablet (mg)** | **82.400** | **164.800** | **329.600** | **100.00** | -- | -- |

q.s: quantity suffucient

Table 8 shows that all three strengths [redacted] (b) (4) active ingredient and inactive excipients.

## B. Comparative dissolution assessment

The Applicant conducted dissolution profiles comparison between Biobatch M590440 and lower strengths in multiple media: water, 0.1N HCl, pH 4.5 Acetate Buffer, and pH 6.8 Phosphate Buffer. The data are listed in Appendix III for details.

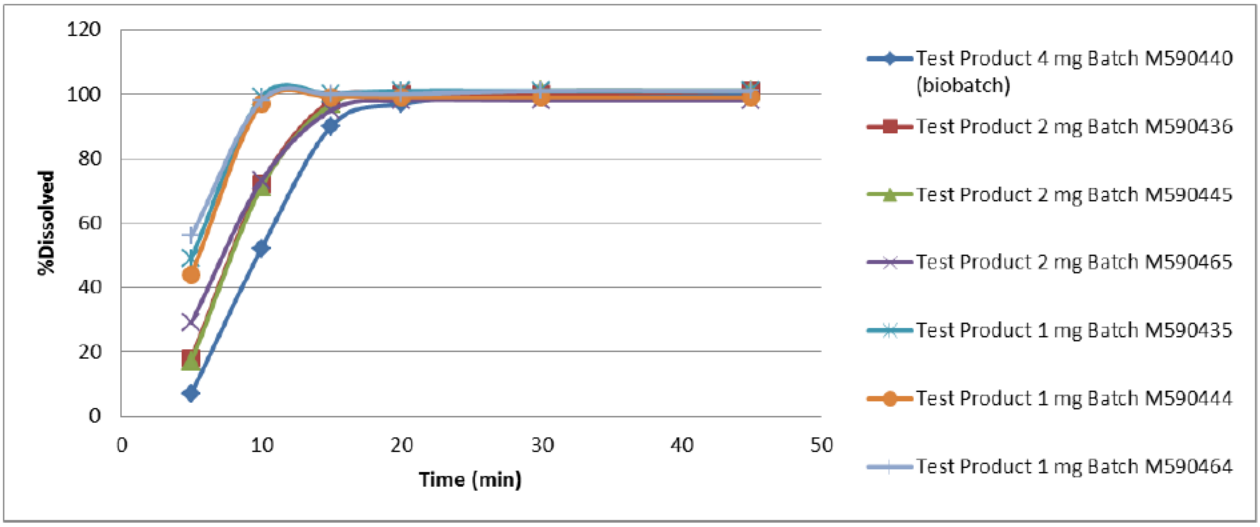
**pH 6.8 Phosphate Buffer** (dissolution method listed in the FDA dissolution database)

Table 9. Mean dissolution data between the highest strength and two lower strengths in pH 6.8 phosphate buffer

| Batch/Time points(min) | 5 | 10 | 15 | 20 | 30 | 45 |
|---|---|---|---|---|---|---|
| Test Product 4 mg Batch M590440 (biobatch) | 7 | 52 | 90 | 97 | 100 | 100 |
| Test Product 2 mg Batch M590436 | 18 | 72 | 98 | 100 | 100 | 101 |
| Test Product 2 mg Batch M590445 | 17 | 71 | 97 | 100 | 101 | 101 |
| Test Product 2 mg Batch M590465 | 29 | 73 | 95 | 98 | 98 | 98 |
| Test Product 1 mg Batch M590435 | 49 | 99 | 100 | 101 | 101 | 101 |
| Test Product 1 mg Batch M590444 | 44 | 97 | 99 | 99 | 99 | 99 |
| Test Product 1 mg Batch M590464 | 56 | 98 | 100 | 100 | 101 | 101 |

The data in Table 9 show that the lower the strength, the faster the initial dissolution, however, all batches have a mean dissolution > 85% at 15 minutes. So they are very rapidly dissolving in pH 6.8 phosphate buffer, and considered to be similar on dissolution profiles without further calculating f2s.

Figure 3. Mean Comparative Dissolution Profiles of Applicant's Biobatch M590440 (4 mg) and its two lower strengths in pH 6.8 phosphate buffer




**Multimedia (water, 0.1N HCl, and pH 4.5 Acetate Buffer)**

Additional dissolution data comparisons were conducted in three other media as shown below.

Table 10. Mean dissolution data between the highest strength and two lower strengths in water

| Batch/Time points(min) | 5 | 10 | 15 | 20 | 30 | 45 |
|---|---|---|---|---|---|---|
| Test Product 4 mg Batch M590440 (biobatch) in water | 17 | 70 | 98 | 101 | 101 | 101 |
| Test Product 2 mg Batch M590436 in water | 25 | 84 | 100 | 100 | 100 | 100 |
| Test Product 1 mg Batch M590435 in water | 43 | 97 | 97 | 97 | 97 | 97 |
| Test Product 4 mg Batch M590440 (biobatch) in 0.1 N HCl | 50 | 96 | 97 | 98 | 97 | 98 |
| Test Product 2 mg Batch M590436 in 0.1 N HCl | 56 | 97 | 97 | 97 | 97 | 97 |
| Test Product 1 mg Batch M590435 in 0.1 N HCl | 83 | 98 | 98 | 98 | 98 | 97 |
| Test Product 4 mg Batch M590440 (biobatch) in pH 4.5 Acetate Buffer | 10 | 51 | 84 | 93 | 99 | 100 |
| Test Product 2 mg Batch M590436 in pH 4.5 Acetate Buffer | 12 | 61 | 94 | 100 | 100 | 100 |
| Test Product 1 mg Batch M590435 in pH 4.5 Acetate Buffer | 38 | 93 | 98 | 99 | 99 | 99 |

The Applicant also used test products to conduct dissolution tests in multimedia. The data in Table 10 show that all batches have a mean dissolution > 85% at 15 minutes in water and 0.1 N HCl. So they are very rapidly dissolving in water and 0.1 N HCl, and considered to be similar on dissolution profiles in water and 0.1 N HCl without calculating f2s.

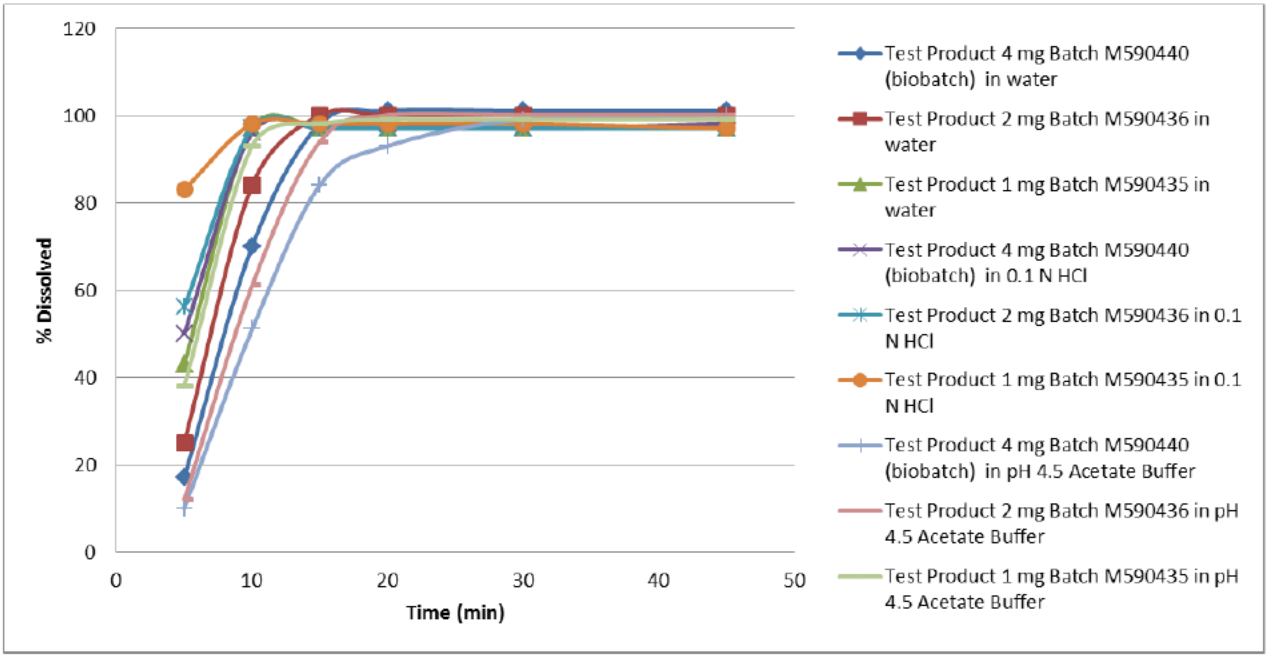
Because Batch M59044 has a mean dissolution of 84% in pH 4.5 Acetate Buffer at 15 minutes, this Reviewer calculated the similarity factors (f2) between the biobatch and lower strengths. It was concluded that Biobatch M590440 and lower strength 2 mg Batch M590436 are similar on dissolution profiles in pH 4.5 Acetate Buffer based on calculated similarity factor, f2=54.03.

However, Biobatch M590440 and lower strength 1 mg Batch M590435 are dissimilar on dissolution profiles in pH 4.5 Acetate Buffer based on the calculated similarity factor, f2=25.96. This Reviewer is of an opinion that the dissimilarity between Biobatch M590440 and lower strength 1 mg Batch M590435 is less satisfactory but acceptable due to the following reasons:

1) Batch M590440 has a mean dissolution of 84% at 15 minutes, which is close to 85%.

2) Pitavastatin Sodium is not stable in pH 4.5 Acetate Buffer. The Dissolution results obtained by the Applicant might not reflect the actual drug release in the dissolution medium (pH 4.5 Acetate Buffer).
3) Biobatch M590440 and lower strength 1 mg Batch M590435 are similar on dissolution profiles in other dissolution media (water, 0.1N HCl, and pH 6.8 Phosphate Buffer)

Figure 4. Mean Comparative Dissolution Profiles of Applicant's Biobatch M590440 (4 mg) and two lower strengths in multimedia




The additional dissolution comparison in other media still showed that the lower the strength, the faster the initial dissolution

**C. Biowaiver**

The Biowaiver is granted for two lower strengths, 2 mg and 1 mg for the following reasons:

1) The lower strength product is in the same dosage form, (i.e., immediate release), but in different strength.

2) The lower strengths (2 mg and 1 mg) and the highest strength (4 mg) (b) (4) in its active and inactive ingredients.

3) The two lower strengths (2 mg and 1 mg) and the highest strength (4 mg) showed consistent dissolution profiles in multimedia.

## R Regional Information

***Comparability Protocols***

**Reviewer's Assessment:**

***Post-Approval Commitments***

**Reviewer's Assessment:**

***Lifecycle Management Considerations***

***List of Deficiencies:***

*None*

***Primary Biopharmaceutics Reviewer Name and Date:***

*Hansong Chen, Pharm.D, Ph.D., 5/22/2017, 7/2/2017*

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

*I concur.  07/16/17*

*Tien-Mien Chen, Ph.D.*

*Acting Biopharm Lead*

*DB/ONDP/OPQ*

Hansong Chen

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Date: 7/17/2017 03:48:40PM
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Tien Mien Chen

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Date: 7/17/2017 04:17:52PM
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# CHAPTER VIII: Microbiology

see Chapter V

# ATTACHMENT I: Final Risk Assessments

See Executive Summary

Su (Suong) Tran

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