CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213260Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

Review # 2 (Class 2 Resubmission)

1. Application/Product Information

NDA Number.	213260		
Applicant Name	CMP Development LLC		
Drug Product Name	ATORVALIQ (atorvastatin calcium) oral suspension		
Dosage Form.	Suspension		
Proposed Strength(s)	4 mg/ml		
Route of Administration	Oral		
Maximum Daily Dose	80 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	To reduce the risk of MI, stroke, revascularization, and angina in adult patients without CHD		
Drug Product Description	The proposed product is a white to brown white, non-sterile, oral suspension packaged in a 180 mL amber glass bottle (fill volume is 150 ml) sealed with a child resistant closure.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	20°C to 25 °C		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Joseph Leginus	Suong Tran
	Drug Product/ Labeling	Akm Khairuzzaman	Mohan Sapru
	Manufacturing	Upsana Sahu	Rose Xu
	Biopharmaceutics	Huong Moldthan	Haritha Mandula

	Microbiology	Yuansha Chen	Nandini Bhattacharya
	Other (specify):	Caryn McNab (ORA)	
	RBPM	Nowrin Kakon, Martin White	
	ATL	Akm Khairuzzaman	
Consults	None		

2. Final Overall Recommendation - *Approval*

3. Action Letter Information

a. Expiration Dating: An expiry dating period of 24 months is granted when the drug product is stored at 20°C to 25°C (68° F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

b. Additional Comments for Action: None

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

1. **Conclusion**: The Office of Pharmaceutical Quality Review team has assessed the NDA 213260 Resubmission with respect to Chemistry, Manufacturing, and Controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that the drug product purports to have. As such, OPQ recommends approval of this NDA from a quality perspective.
2. **Background**: A complete response (CR) was issued on 10/16/2020 due to objectionable conditions at the manufacturing facility namely, (b) (4) Additionally, instructions were provided to the Applicant to revise their commercial manufacturing batch records with respect to specific process parameters and in-process control ranges[1]. The Applicant has resubmitted their NDA on 8/1/2022.
3. **Summary of the resolution of deficiencies and the review for each OPQ discipline:**
    I. **Drug substance**: The drug substance was found to be acceptable during the first review cycle of this NDA. The applicant provided reference to DMF (b) (4) for all chemistry manufacturing and control (CMC) information related to the drug substance. During the review of this resubmission, the drug substance reviewer, Dr.

[1] Refer to the Integrated Quality Review (IQA) # 1 in DARRTS dated 10/5/2020 (filed by Dr. Muthukumar Ramaswamy) for previous recommendation history.

Joseph Leginus asked the Applicant for inclusion of a test for particle size distribution with three tier limits in the drug substance specification. On 9/13/2022 the Applicant updated the drug substance specification to include particle size distribution with justification and validated analytical method. Dr. Leginus' s review concludes that the CMC information provided in the NDA resubmission and DMF is adequate and there are no additional drug substance related deficiencies that need to be reported to the applicant. A retest date of (b) (4) months is granted for atorvastatin calcium when stored at (b) (4) in (b) (4)

II. **Drug Product:** From drug product perspective, no pending issues were communicated through the CR letter. The dosage form is an oral suspension, suitable for patients with dysphagia. The drug product contains the drug substance and other inactive ingredients namely: carboxymethylcellulose sodium, methyl para-(b) (4)ben(b) (4), ethyl para(b) (4)ben(b) (4), propyl para-(b) (4)ben(b) (4), (b) (4) (magnesium aluminum silicate), sucralose, acesulfame potassium, and orange flavor ((b) (4) (b) (4) The product is available as 4 mg/ml strength, supplied in 180 mL Amber Glass Bottles with White Child Resistant Closures. Additional CMC data from a newly manufactured drug product batch (dosed in the new BE study) is submitted in this NDA resubmission. Dr. Khairuzzaman' s review concludes that the formulation composition, manufacturing process and quality standards remains unchanged. Additionally, the particle size distribution of the drug substance lot used in the new BE batch also remains the same. Therefore, the drug product reviewer, Dr. Khairuzzaman' s original recommendation (i.e., adequate) for this NDA remains unchanged. Based on the previously submitted stability data and new data submitted in this resubmission, the drug product is granted a 24-month expiry when stored at controlled room temperature. The drug product should be stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 5°C to 30°C (59°F to 86°F).

III. **Manufacturing**: *Process*: The applicant has satisfactorily responded to the office of Pharmaceutical Manufacturing Assessment (OPMA/OPQ) Reviewer's recommendation in the CR letter and updated the commercial batch records with respect to

process parameters and in-process control ranges and equipment to be used for commercial manufacturing. This is now acceptable. *Facilities*: The objectionable facility (the [redacted] facility) as communicated in the CR letter has been withdrawn in this NDA resubmission. The Applicant transfers the responsibilities to [redacted]. These new facilities, as well all other facilities are compliant. Therefore, the office of Pharmaceutical Manufacturing Assessment (OPMA/OPQ) has recommended "approval" for these newly listed facilities.

IV. **Quality labeling:** The quality aspects of the labeling submitted in the resubmission are reviewed and found to be adequate.

V. **Microbiology**: There is no change in microbiology in this NDA resubmission. The Microbiology quality for this NDA resubmission was reviewed and deemed adequate in the last review cycle and remains as adequate.

VI. **Biopharmaceutics**: Biopharmaceutics review was adequate in the previous cycle of the original submission. Dr. Huong's review on this resubmission concludes that the proposed quality control dissolution specification (method and criterion) remains unchanged, and it can discriminate towards critical material attributes (CMAs) and critical formulation variables (CFVs). Dr. Dr. Huong's review also concludes that the newly submitted dissolution data from the new bio-batch meets the established criterion. Finally, Dr. Huong's review concludes that the drug substance particle size distribution used in this newly manufactured bio-batch is very similar with that of the previously dosed bio-batch.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Choose an item.

QPA for EA(s): Yes

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments: None

Comparability Protocols (PACMP): No
Comments: None

Additional Lifecycle Comments: Atorvastatin calcium is a poorly soluble drug substance, and the drug product is an oral suspension. Therefore, any change in the drug substance particle size distribution and polymorphism may require appropriate bridging to establish bioequivalence and a prior approval supplement (PAS).

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Items	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	ATORVALIQ® (atorvastatin calcium) oral suspension	Acceptable. Follows USP monograph of the marketed tablet dosage form.
Established name(s)	atorvastatin calcium oral suspension	Acceptable
Route(s) of administration	Oral	Acceptable
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	4 mg/mL	Acceptable Strength is expressed as base. Follows USP monograph of the marketed tablet dosage form.
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Not a parenteral drug product	Acceptable
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	None	Acceptable
Available dosage form(s)	Oral suspension	Acceptable

Strength(s) in metric system	4 mg/ml	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	The strength is expressed as atorvastatin base as per the USP monograph for the marketed tablet dosage form	Acceptable

1.2.3 Section 11 (DESCRIPTION)

Items	**Information Provided in the NDA**	**Assessor's Comments**
DESCRIPTION section		
Proprietary and established name(s)	Atorvaliq (Atorvastatin Calcium) Oral Suspension	Acceptable
Dosage form(s) and route(s) of administration	Suspension, oral	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	The strength is expressed as atorvastatin base as per the USP monograph for the marketed tablet dosage form	Acceptable
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Provided	Needs revision in the PI to rearrange alphabetically.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Not a parenteral drug product	Acceptable
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Not Applicable	Acceptable
Statement of being sterile (if applicable)	Not Applicable	Acceptable
Pharmacological/ therapeutic class	Yes	Acceptable
Chemical name, structural formula, molecular weight	Yes	Acceptable
If radioactive, statement of	Not Applicable	Acceptable

important nuclear characteristics.		
Other important chemical or physical properties (such as pKa or pH)	None	Acceptable
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity	None present	Acceptable

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Items	**Information Provided in the NDA**	**Assessor's Comments**
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Oral suspension	Acceptable
Strength(s) in metric system	4 mg/ml	Acceptable
Available units (e.g., bottles of 100 tablets)	150 ml in a bottle	Acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Its an oral liquid dosage form. Description of the formulation has been provided.	Acceptable
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient use). Other package terms include pharmacy bulk package and imaging bulk package.	Not an injectable dosage form	Acceptable
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	None	Acceptable

Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at room temperature [20°C to 25°C (68° F to 77°F)], excursions permitted to 15°C to 30°C (59° F to 86°F)	Acceptable
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex free."	Not Applicable	Acceptable
Include information about child-resistant packaging	Not Acceptable	Acceptable

1.2.6 Manufacturing Information After Section 17 (for drug products)

Items	Information Provided in the NDA	Assessor's Comments
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Distributed by CMP Pharma Inc. (b) (4) Farmville, NC 27828	Acceptable

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): No CMC related information.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)

Items	Information Provided in the NDA	Assessor's Comments
Proprietary name, established name, and dosage form (font size and prominence	ATORVALIQ® (atorvastatin calcium) oral suspension	Acceptable
Dosage strength	4 mg/ml	Acceptable
Route of administration	oral	Acceptable
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Follows approved USP product for the LD	Acceptable
Net contents (e.g. tablet count)	150 ml per bottle	Acceptable
"Rx only" displayed on the principal display	yes	Acceptable
NDC number	yes	Acceptable
Lot number and expiration date	yes	Acceptable
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 20°C to 25°C (68° F to 77°F), excursions permitted to 15°C to 30°C (59° F to 86°F)	Acceptable
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single patient-use)	Not an injectable dosage form	Acceptable

Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	Not applicable	Acceptable
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	No alcohol in formulation	Acceptable
Name of manufacturer/distributor	Distributed by: CMP Pharma Inc. Farmville, NC 27828 USA	Acceptable
Medication Guide (if applicable)	Instruction of (b) (4) has been provided on the bottle labeling.	Acceptable
No text on Ferrule and Cap Overseal	Not Applicable	Acceptable
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	The strength is expressed as atorvastatin base as per the USP monograph for the marketed tablet dosage form	Acceptable

Assessment of Carton and Container Labeling: *Adequate*

ITEMS FOR ADDITIONAL ASSESSMENT

1. The inactive ingredient list in section 16 need to be revised alphabetically.

Overall Assessment and Recommendation: **Adequate after the above deficiencies are fulfilled.**

Primary Drug Product Assessor Name and Date: Akm Khairuzzaman, Ph.D., 8/19/2020.

Secondary Assessor Name and Date (and Secondary Summary, as needed): Mohan Sapru, Ph.D., 8/19/2020.

Akm Khairuzzaman

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Mohan Sapru

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MICROBIOLOGY

Product Background:

NDA: 213260

Drug Product Name / Strength: Atorvastatin Oral Suspension, 4 mg/mL, multi dose

Route of Administration: Oral

Applicant Name: CMP Development LLC

Manufacturing Site: (b) (4)

Method of Sterilization: N/A, drug product is non-sterile

Review Recommendation: Drug product is recommended for approval based on Microbiological quality

Review Summary:

List Submissions Being Reviewed:

Submitted	Received	Assigned to Reviewer
8/1/2022	8/1/2022	8/2/2022

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: eCTD

Concise Description Outstanding Issues Remaining: None

Supporting Documents: N/A

List Number of Comparability Protocols: N/A

Product Quality Microbiology Assessment

The amendment submitted in 8/1/2022 provided response to the Agency's CR letter dated 10/16/2020. The amendment provided no new information pertaining to microbiology quality of the drug product. Microbiology quality for this NDA was reviewed and deemed adequate in the last review cycle and remains as adequate. Please refer to microbiology review N213260MR01.doc dated 7/6/2020 for details.

List of deficiencies:
None

Primary Microbiology Reviewer Name and Date:

Yuansha Chen, Ph.D.

CDER/OPQ/OPMA/DMA

10/12/2022

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

Nandini Bhattacharya, Ph.D.

CDER/OPQ/OPMA/DMA

10/12/2022

Yuansha Chen

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Nandini Bhattacharya

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CHAPTE VI: BIOPHARMACEUTICS

IQA NDA Assessment Guide Reference

Product Information	Atorvastatin Oral Suspension
NDA Number	NDA-213260-ORIG-1-RESUB-17
Assessment Cycle Number	1
Drug Product Name/ Strength	Atorvaliq (Atorvastatin Calcium)/ 4 mg/mL
Route of Administration	Oral
Applicant Name	CMP Development LLC
Therapeutic Classification/ OND Division	Lipid Altering Agents / CDER/OCHEN/DDLO
RLD/RS Number	NDA-202702 (Lipitor)
Proposed Indication	It is an HMG-CoA reductase inhibitor indicated as an adjunct therapy to diet to reduce the risk of MI, stroke, revascularization, and angina in adult patients within CHD, but with multiple risk factors.

Assessment Recommendation: **Adequate**

Assessment Summary:

CMP Development LLC (Applicant) is seeking approval of Atorvastatin Oral Suspension 4 mg/mL (20 mg/5 mL), which was originally submitted on 01/13/ 2020 under NDA-213260 via the 505(b)(2) pathway using LIPITOR (atorvastatin calcium) oral tablet 80 mg as the listed drug (LD). The submission received a Complete Response Letter (CRL) dated 10/16/2020 due to deficiencies from several disciplines other than Biopharmaceutics. In the CRL's response which was received on 08/01/2022, the Applicant manufactured a new biobatch with the same formulation, same particle distribution (PSD) and the same manufacturing process. The dissolution studies of the new biobatch and listed drug (LD) were performed using the approved dissolution method indicated similarity. The Applicant conducted an in vivo bioequivalence study comparing the LD and the proposed drug.
Early IR was sent on 08/31/2022[1] requesting additional details regarding drug substance particle size distribution and if in vitro drug release method can discriminate the API particle size.
The Applicant's responses are satisfactory (IRs, Responses, and Assessment are detailed under the section "BIOPHARMACEUTICS LIST OF DEFICIENCES"). The proposed quality control dissolution specification (method and criterion) is discriminating towards critical material attributes (CMAs) and critical formulation variables (CFVs) and is found acceptable.

[1] \\CDSESUB1\EVSPROD\nda213260\0018\m1\us\1-2-cover-letters\1-2-2-cover-letters.pdf

Table 1. Dissolution Method for Atorvastatin Oral Suspension (4mg/mL i.e.,20mg/5mL)

Apparatus	Agitation Speed (rpm)	Dissolution Medium/Temperature	Dissolution Medium Volume (mL)	Dissolution Acceptance Criterion
USP II (Paddle)	75	0.05 M Phosphate buffer, pH 6.8 at 37°C ± 0.5°C	900	NLT (b)(4)% (Q) in 15 min
* 20mL of sample suspension of 4mg/mL (equivalent to 80mg drug) is used for dissolution testing which represents highest recommended clinical dose				

List Submissions being assessed (table):

Document(s) Assessed	Date Received
0016 (17): Resubmission **0021 (11): Response to IR**	**08/01/2022** **09/13/2022**

Highlight Key Issues from Last Cycle and Their Resolution:

Biopharmaceutics review was adequate in the previous cycle of the original submission. However, the submission received Complete Response Letter (CRL) dated 10/16/2020 due to the deficiencies from several disciplines, including the failure to meet the requirements of comparative bioavailability between the proposed drug product and the listed drug.

Concise Description of Outstanding Issues (Deficiency from Clinical Pharmacology Review)

"Since the application does not contain clinical efficacy and safety data for the proposed atorvastatin calcium oral suspension (proposed product), relative bioavailability results are the fundamental bridge to the efficacy and safety data of the listed drug product. Relative bioavailability between the proposed product and the listed drug did not meet the conventional 80 – 125% criteria based on results from Study 18-VIN-0235. The 90% confidence interval for the geometric mean ratios (GMRs) between the proposed product and the listed drug for all primary PK parameters (AUC0-t, AUC0- and Cmax) were outside the conventional 80 – 125% limits for all moieties measured (atorvastatin, 2-hydroxy atorvastatin, and 4-hydroxy atorvastatin) under fasting conditions. The exposures of atorvastatin, 2-hydroxy atorvastatin, and 4-hydroxy atorvastatin were (b) (4) *respectively following administration of the proposed product as compared to those following administration of the listed drug. In addition, results from Study 18-VIN-0236 indicate that the proposed product had a greater magnitude of food effect (30% reduction in AUC and 63% reduction in Cmax) compared to the reported values of 9% reduction in AUC and 25% reduction in Cmax for the listed drug when administered with food. The deficiency cannot be addressed with labeling because there is no condition of use that would ensure safety and effectiveness of the product. When the proposed product is administered under fed conditions, the magnitude of the decrease in atorvastatin and its metabolites exposure is much greater for the proposed product compared to the listed drug, which could lead to loss of efficacy. On the other hand, if the product is administered under fasting conditions, the large increase in atorvastatin and its metabolites exposure compared to*

the listed drug is a safety issue. Additionally, there is a wide fluctuation in atorvastatin and metabolite levels following administration of the proposed product compared to the listed drug under both fasting and fed conditions. Thus, the clinical pharmacology and other relevant findings of the listed drug cannot be relied upon for the proposed atorvastatin product and the data do not support its approval.
INFORMATION NEEDED TO RESOLVE DEFICIENCIES:
Reformulate the proposed product and conduct additional relative bioavailability studies to demonstrate the bioequivalence to the listed drug or conduct a clinical study to support the effective and safe use of the proposed atorvastatin oral suspension product"

B.1 BCS DESIGNATION

Assessment:

Solubility: Freely soluble in methanol, slightly soluble in alcohol, very slightly soluble in distilled water, in pH 7.4 phosphate buffer, and in acetonitrile, insoluble in aqueous solutions of pH 4 and below. The Applicant stated that the drug substance belongs to BCS Class II.

Table 2. Solubility in Different Solvents at About 37°C

	Dissolution Media	Solubility (mg /ml)
Saturation solubility at 37°C	Water	0.14
	Phosphate Buffer pH 6.8	0.31
	Acetate Buffer pH 4.5	0.07
	0.1N HCl	0.02 (Degradation)

Permeability: Not provided

Dissolution: API solubility has direct impact on the dissolution of the product. The initial risk is medium.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: *{Adequate}*

Table 3. Approved Dissolution Method and Acceptance Criterion for Quality Control of the Proposed Atorvastatin Suspension [4mg/mL (20mg/5mL)]

Dissolution Conditions	Apparatus	USP II (paddle)
	Speed of Rotation	75 rpm
	Medium	0.05 M Phosphate buffer, pH 6.8
	Volume	900 mL

	Temperature	37°C ± 0.5°C
Proposed Acceptance Criterion	NLT (b) (4)% (Q) in 15 minutes	

The Applicant performed the dissolution studies on a new biobatch (ATV21001). The Average percentage drug release in the reference product (Lipitor® 80mg tablets) is lower than that of test product (Atorvastatin oral suspension 4mg/L) at the sampling timepoints of 5 minutes and 10 minutes. After 10 minutes, for the other time points (15 minutes, 20minutes, 30minutes, 45minutes and 60 minutes), the Average % drug release of test product (Atorvastatin oral suspension 4mg/L) and LD was found to be comparable. (Figure 1)

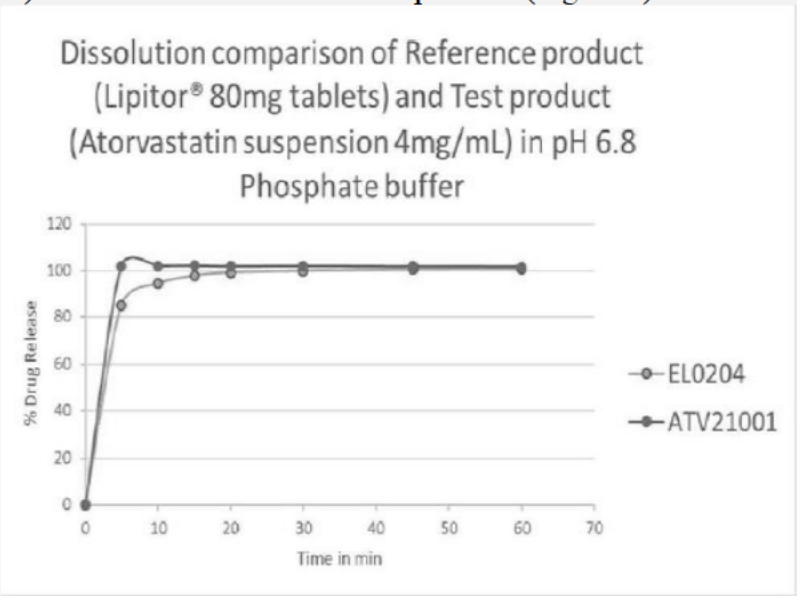

Figure 1. Dissolution comparison of Reference product (Lipitor® 80mg tablets) and Test product (Atorvastatin suspension 4mg/mL) using the approved dissolution method

Table 5. Drug substance lot AC1m1640917 was used to manufacture the new bio batch (ATV21001) as well as the previous bio batch (VAL/18/0073/B).

Lot #	Results					
	MSN D_{10}	LM D_{10}	MSN D_{50}	LM D_{50}	MSN D_{90}	LM D_{90}
AC1m0600614	(b) (4)					
AC1m0080119						
AC1m0830716						
AC1m1640917						
AC1m1690917						

B.3 CLINICAL RELEVANCE OF DISSOLUTION METHOD & ACCEPTANCE CRITERIA *(e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)*

Assessment: ***{Pending}***

The evaluation on clinical relevance of dissolution method and acceptance criterion are separately assessment by Clinical Pharmacology Reviewer.

B.12 BRIDGING OF FORMULATIONS

Assessment: ***{Adequate}***

In Vitro bridging is not needed as the manufacturing site for commercial batch is same as the one used for biobatch manufacturing. (Manufacturing site for both the submission and commercial batches of the finished drug product are at (b) (4) (b) (4) (b) (4)

BIOPHARMACEUTICS LIST OF DEFICIENCIES

Comment 1
Provide information on the drug substance particle size distribution as follows:
a. Drug substance particle size distribution for the lot used to manufacture the new biobatch # ATV21001

Applicant's Response

Drug substance lot AC1m1640917 (DS Manufacturer lot #) was used to manufacture the new bio batch (ATV21001) as well as the previous bio batch (VAL/18/0073/B). LM's Certificates of Analysis for drug substance lots AC1m1640917 and AC1m1690917 have been updated to include particle size results with three tier limits and are presented within Section 3.2.S.4.4.

b. Data to show if the in vitro drug release method can discriminate the API particle size differences

Applicant's Response

Comment 2
Include a test for drug substance particle size distribution with three tier limits in the drug substance specification. Provide appropriate justification for the proposed limit.

Applicant' Response

Provided below in Table 1 is a summary of particle size results obtained from various lots of drug substance tested during drug product development, validation, and registration batch manufacture.

Particle Size Distribution Test	Specifications
D_{10}	(b) (4)
D_{50}	
D_{90}	

Reviewer's Assessment

The Applicant provided sufficient information for the requested deficiency comments. Therefore, the response is adequate.

Primary Biopharmaceutics Assessor's Name and Date: Huong Moldthan, Ph.D. (11/03/2022)

Secondary Assessor Name and Date (and Secondary Summary, as needed): Haritha Mandula, Ph.D. (11/27/2022)

Huong Moldthan

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Haritha Mandula

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/s/

AKM KHAIRUZZAMAN
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The OPQ review team recommends approval of this NDA from a quality perspective

QUALITY ASSESSMENT

Recommendation: Complete Response

NDA 213260
Review 1

Drug Name/Dosage Form	(b) (4) (atorvastatin calcium) oral suspension
Strength	4 mg/mL
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	CMP Development LLC
US agent, if applicable	-

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original submission, and amendments	Original submission: 1/13/2020 Amendments: 3/13/2020, 5/22/2020, 6/8/2020, 7/1/20, 7/02/2020, 7/07/2020, 8/06/20, 8/27/20, and 9/9/20.	Quality modules 3, 1.14, and 1.11

Quality Review Team

Discipline	Reviewer/Secondary	Branch/division
Drug Substance	Joseph Leginus/ Suong Tran	Branch III/Division of New Drug API/Office of New Drug Products (ONDP)
Drug Product	Akm Khairuzzaman / David J Claffey	Branch V/Division of New Drug Products III/ONDP
Process/ Facility	Upasana Sahu/Kumar Janoria	Branch II/ Office of Pharmaceutical Manufacturing Assessment (OPMA)
Microbiology	Yuansha Chen/ Nandini Bhattacharya	Division of Microbiology Assessment/OPMA
Biopharmaceutics	Huang Moldthan/Poonam Delvadia	Division of Biopharmaceutics/ ONDP
Regulatory Business Process Manager	Leeza Rahimi/ Hamet Toure	Branch I/Regulatory Business Process Management I
Application Technical Lead	Muthukumar Ramaswamy	Branch V/Division of New Drug Products III/ONDP
Environmental Analysis (EA)	Akm Khairuzzaman / David J Claffey	Branch V/Division of New Drug Products III /ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)		Active	3/30/20	LOA dated 7/5/2019
	III			Active	*	LOA dated 3/19/2019
	III			Active	*	LOA dated 3/25/2019
	IV			Active	*	LOA 10/4/019

*Sufficient information provided in the NA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	137915	Atorvastatin calcium oral suspension

2. CONSULTS: None

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Pharm./Tox. – Limit for impurities	Completed	Acceptable	May 12, 2020	Dr. Lydia Hallie

Executive Summary

I. Recommendations and Conclusion on Approvability

The Office of Pharmaceutical Quality (OPQ) recommends a **complete response** action due to deficiencies related to process and facilities (specifically related to (b) (4) , the drug product manufacturing site and (b) (4) the drug substance testing site).

Summary of Complete Response Issues
Facility: The drug product is manufactured at (b) (4) . Based on the review of records obtained from (b) (4) through 704(a)(4) records request process, the facility review team identified deficiencies related to (b) (4) The facility review team concluded that a satisfactory pre-approval inspection and/or adequate facility responses addressing these conditions is needed before this application may be approved. A withhold approval recommendation is enetered by OPMA for this facility in Panorama.

The drug substance testing facility, (b) (4). is currently under the OAI. The facility will be put on withhold for this review cycle. The facility compliance status will be re-evaluated in the next review cycle.

The overall manufacturing inspection recommendation (OMIR) from the Office of Process Manufacturing Assessment (OPMA) for this NDA in Panorama is "withhold approval".

Process: The proposed commercial (b) (4) batch records provided in module 3.2.P.3.3 currently does not contain any specific (b) (4)

Thus, the overall recommendation for process and facilities from OPMA for this NDA is inadequate.

Action Letter Approvability Deficiencies:

Process:

1. The proposed commercial (b) (4) batch records provided in module 3.2.P.3.3 currently does not contain any specific (b) (4) Please revise the submitted (b) (4) batch records to clearly prescribe the proposed ranges of all critical process parameters (b) (4) Update 3.2.P.3.3 accordingly.

Facility:

1. During a review of records requested under section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act, and provided by [redacted](b) (4) manufacturing facility, the FDA noted objectionable conditions. These objectionable conditions will be conveyed to the representative of the facility within 10 business days of this Complete Response Letter. Satisfactory resolution of these objectionable conditions is required (e.g., preapproval inspection and/or adequate facility responses addressing these conditions) before this application may be approved.

   If it is determined that an inspection is needed to approve your application, please note that FDA continues to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections, once safe travel may resume and based on public health need and other factors.

   For more information, please see the FDA guidances related to COVID 19. These guidances can be found at https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders

2. During a recent inspection of the [redacted](b) (4) manufacturing facility, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this NDA may be approved. Please list communications submitted to, or held with, the Agency to facilitate resolution of the observed objectionable conditions, or deficiencies, noted at the facility.

Additional comments

We acknowledge the environmental analysis submitted under the eCTD module section 1.12.14. Per the 21 CFR 314.50 (d) (l) (iii), an environmental assessment exemption request should be completed as per the CFR § 25.30 or 25.31 or § 25.40. Therefore, resubmit your environmental assessment exception request accordingly.

II. Summary of Quality Assessments

A. Product Overview

The proposed 505(b)(2) application is for atorvastatin calcium oral suspension. This 505(b)(2) NDA references Lipitor (atorvastatin calcium) tablets 80 mg as the listed drug (NDA 020702). [redacted](b) (4) (atorvastatin calcium) oral suspension, 4 mg/mL is a white to brownish white suspension. Each mL of oral suspension contains atorvastatin calcium

equivalent to 4 mg atorvastatin. The proposed indication includes prevention of cardiovascular disease and hyperlipidemia (see below, proposed indication section).

The oral suspension is supplied in a150 mL amber glass bottle with child resistant closure. The drug product should be stored at 20°C to 25°C (68°F to 77°F). Excursions permitted between 15°C and 30°C (59°F and 86°F).

Proposed Indication(s) including Intended Patient Population	(b) (4) is an HMG-CoA reductase inhibitor indicated as an adjunct therapy to diet to: • Reduce the risk of myocardial infarction (MI), stroke, revascularization procedures, and angina in adult patients without coronary heart disease (CHD), but with multiple risk factors • Reduce the risk of MI and stroke in adult patients with type 2 diabetes without CHD, but with multiple risk factors • Reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for congestive heart failure (CHF), and angina in adult patients with CHD • Reduce elevated total cholesterol (total-C), low-density lipoprotein-C (LDL-C), apo B, and triglyceride (TG) levels and increase high-density lipoprotein-C (HDL-C) in adult patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia • Reduce elevated TG in adult patients with hypertriglyceridemia and primary dysbetalipoproteinemia • Reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH) • Reduce elevated total-C, LDL-C, and apo B levels in pediatric patients, 10 years to 17 years of age, with heterozygous familial hypercholesterolemia (HeFH) after failing an adequate trial of diet therapy
Duration of Treatment	Chronic
Maximum Daily Dose	80 mg
Alternative Methods of Administration	Not applicable

B. Quality Assessment Overview

Drug Substance

The applicant provided reference to DMF (b) (4) for all chemistry manufacturing and control (CMC) information related to the drug substance. The chemical name for the atorvastatin calcium is calcium (βR, δR)-2-(p-fluorophenyl)-β,δ-dihydroxy-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)pyrrole-1-heptanaote (1:2), trihydrate The molecular formula and molecular weight of the drug substance is respectively $(C_{33}H_{34}FN_2O_5)_2Ca$.

$3H_2O$ and 1209.4 g/mol. The drug substance is crystalline. The drug substance is practically insoluble in water at pH1.2 to 8.0. Dr. Joseph Leginus reviewed the CMC information provided in the DMF as well as in the NDA.

Per drug substance reviewer, the proposed atorvastatin calcium release testing is consistent with the USP monograph. The applicant also performs additional testing for residual solvents, XRD, and (b) (4) content. Dr. Leginus's review concluded that the CMC information provided in the NDA and DMF is adequate and there are no drug substance related deficiencies that need to be reported to the applicant. Based on stability data review, Dr. Leginus granted a retest period of (b) (4) months for atorvastatin calcium drug substance, when stored (b) (4) C. For additional details, please refer to Dr. Leginus' s CMC review dated 3/31/2020 in Panorama.

Drug Product

The proposed product is a white to brown white, non-sterile, oral suspension packaged in a 150 mL amber glass bottle sealed with a child resistant closure. Each mL of atorvastatin calcium oral suspension contains the equivalent of 4 mg atorvastatin. The drug product also contains the following excipients: carboxymethylcellulose sodium, methyl para (b) (4) ben (b) (4), ethyl para (b) (4) ben (b) (4), propyl para (b) (4) ben (b) (4), (b) (4) (magnesium aluminum silicate), sucralose, acesulfame potassium, and orange flavor. The composition of the proposed commercial product is the same as the one used in BE studies. The drug product is easily resuspendable with minimum effort. The proposed excipients are compendial grade or known for use in approved products.

Dr. Akm Khairuzzaman reviewed the drug product information including drug product composition, drug product specification including assay and limits proposed for impurities, excipient information, analytical methods, container closure system, compatibility information, and stability data, and environmental assessment (EA). The applicant requested exemption from environmental assessment per 21 CFR 314.50 (d) (l) (iii). Since EA exemption can only be granted per 21CFR 25.30 or 25.31 or 25.40. The applicant will be asked to resubmit the environmental assessment information for further consideration in the next review cycle.

The drug product is tested for appearance, identity, (b) (4) content, pH, assay, purity and impurities, deliverable volume, uniformity of dosage units, sedimentation volume, and zeta potential. Dr. Khairuzzaman's review concluded that the proposed drug product specification is adequate. The drug product reviewer also performed a risk assessment for critical attributes and concluded that the final risk is low for the proposed product.

The application contains 24 months of long-term and intermediate storage stability data (25°C/60% RH and 30°C/65% RH) and 6 month accelerated stability (40°C/65% RH), for 3 primary stability batches manufactured at (b) (4). Based on intermediate storage stability data, the drug product reviewer granted an expiration period of 24 months for the product, when stored at 20°C to 25°C (68°F to 77°F) in commercial packaging. Dr. Khairuzzaman's overall recommendation for this NDA is adequate. Please refer to the

Dr. Khairuzzaman's drug product review dated 9/4/20 for additional information. The CMC labeling review for this NDA will be completed in the next review.

Microbiological control information: Microbiology reviewer, Dr. Yuansha Chen reviewed the microbiological controls information including drug product specification. The drug product is tested microbial enumeration test (USP <61>), total aerobic count, total yeast and mold (USP <62>) and for specified organisms *E. coli* and *Burholderia cepacia complex* (USP <1111>). The drug product specification includes antimicrobial effectiveness test (USP <51>). Dr. Chen's review concluded that the proposed microbiological controls are adequate and recommended approval of the NDA. For details, please refer to Dr. Chen's review dated 7/09/2020 in Panorama.

Biopharmaceutics: The drug substance (API) belongs to BCS Class II (low solubility, high permeability). Dr. Huang Moldthan reviewed the dissolution method information, method development information (i.e., method's discriminating ability to detect changes in critical material attributes and formulation variables), and dissolution acceptance criteria. Dr. Moldthan's review concluded that the NDA contains adequate biopharmaceutics information and her recommendation for this NDA is adequate. Since the dissolution information for pilot BE study batches was not available, the biopharm reviewer also concluded that clinical relevance of the dissolution method cannot be determined at this time. Please refer to Dr. Moldthan 's review dated 9/28/20 in Panorama.

Manufacturing Process and Facility: Dr. Upasana Sahu reviewed the process/facility information. The proposed commercial batch size is (b) (4) The composition of the drug product, the drug product manufacturing process, and the packaging system used to manufacture the drug product used in BE studies are the same as that proposed for commercial use. The manufacturing process involves (b) (4) .

(b) (4) Her review concluded that the proposed commercial (b) (4) batch records are inadequate to support the NDA. The following process deficiency will be conveyed in the action letter.

> *The proposed commercial* (b) (4) *batch records provided in module 3.2.P.3.3 currently does not contain any specific* (b) (4)

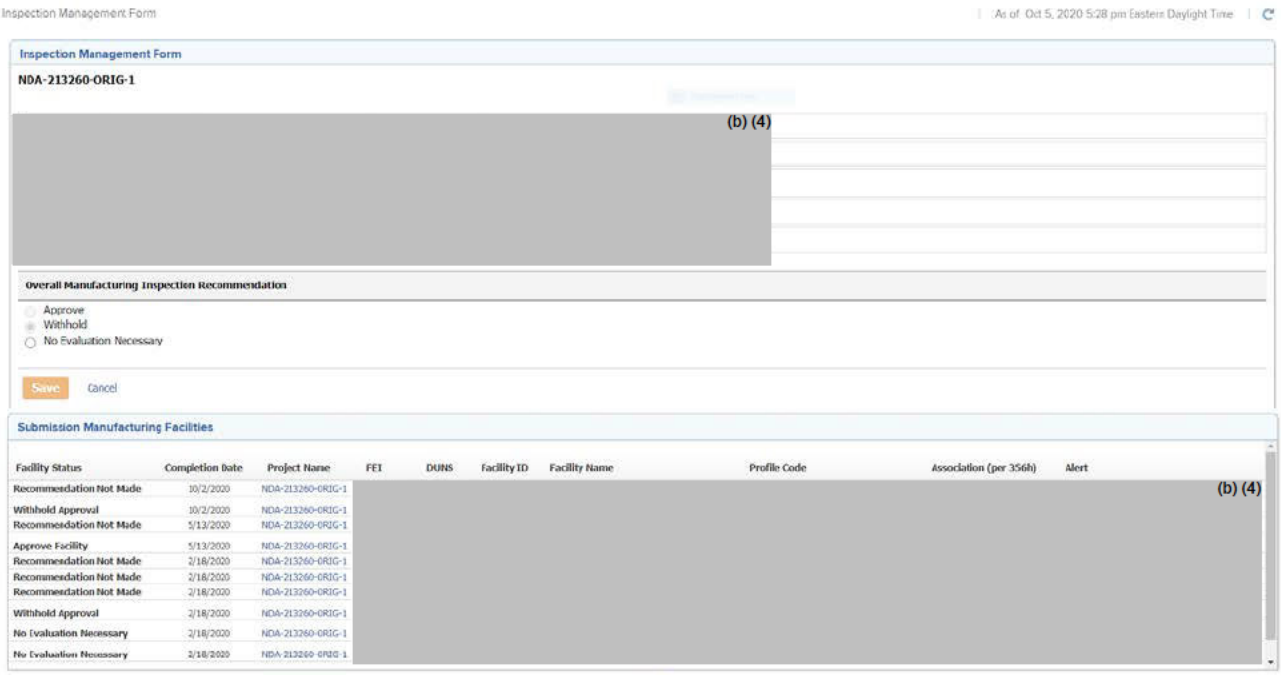
(b) (4)

Facility compliance information for the drug product and drug substance manufacturing and testing facilities was reviewed by facility review team (OPMA/ORA). Their review concluded that the compliance status of the drug substance manufacturing facility ((b) (4)) is acceptable. The facility review team recommended withhold approval recommendation to (b) (4), the drug substance testing facility and (b) (4) the drug product manufacturing facility for the following reasons:

(1) (b) (4) is currently under OAI.

(2) (b) (4) 704(4)(a) record review process identified deficiencies that include issues related to (b) (4) . The facility team review concluded that a satisfactory pre-approval inspection and/or adequate facility responses addressing these objectionable conditions is needed before this application may be approved.

The overall manufacturing inspection recommendation (OMIR) from the Office of Process Manufacturing Assessment (OPMA) for this NDA is withhold approval. The Panorama screen shot of the facility assessment recorded on 10/5/2020 is shown below. For additional details, please refer to Dr. Sahu's facility review in Panorama dated 10/5/2020.



OVERALL ASSESSMENT AND SIGNATURES:

At present, there are no outstanding deficiencies related to the drug substance, drug product, biopharmaceutics, and microbiology sections of the NDA. The applicant will be asked to resubmit the environmental assessment. Due to outstanding manufacturing process and facility related deficiencies, the OPQ overall recommendation for NDA *213260 is complete response.*

Muthukumar Ramaswamy, Ph.D. 10/5/2020

Application Technical Lead Name and Date

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MICROBIOLOGY

Product Background:

NDA: 213260

Drug Product Name / Strength: Atorvastatin Oral Suspension, 4 mg/mL, multi dose

Route of Administration: Oral

Applicant Name: CMP Development LLC

Manufacturing Site: (b) (4)

Method of Sterilization: N/A, drug product is non-sterile

Review Recommendation: Drug product is recommended for approval based on Microbiological quality

Review Summary:

List Submissions Being Reviewed:

Submitted	Received	Assigned to Reviewer
1/13/2020	1/13/2020	1/23/2020
5/22/2020	5/22/2020	N/A (IR response)
7/2/2020	7/2/2020	N/A (IR response)

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: eCTD

Concise Description Outstanding Issues Remaining: None

Supporting Documents: N/A

List Number of Comparability Protocols: N/A

Product Quality Microbiology Assessment

All of the information in this review relates to patient risk associated with a non-sterile liquid suspension for oral administration.

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – White to brownish white suspension packaged in a 150 mL Amber Glass Bottle with White Child Resistant Closure.
- **Drug product composition** –

Component	Function	Quantity in mg per mL of Suspension
Atorvastatin (as Atorvastatin Calcium Trihydrate)	API	4.00
Carboxymethylcellulose Sodium		(b) (4)
Magnesium Aluminum Silicate		
Methylparaben		
Ethylparaben		
Propylparaben		
Sucralose		
Acesulfame Potassium		
Orange Flavor ((b) (4)		
(b) (4) Water		

- **Description of container closure system** –

Component	Description	
Bottle	(b) (4)	
Cap		

Reviewer's Assessment:
The drug product composition and container-closure system were adequately described.

ADEQUATE

Yuansha Chen

Digitally signed by Yuansha Chen
Date: 7/07/2020 10:48:22AM
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Nandini Bhattacharya

Digitally signed by Nandini Bhattacharya
Date: 7/09/2020 07:04:15AM
GUID: 508da70c00028f454473851fced0e9d4

CHAPTE VI: BIOPHARMACEUTICS

IQA NDA Assessment Guide Reference

Product Information	Atorvastatin Oral Suspension
NDA Number	NDA-213260-ORIG-1
Assessment Cycle Number	1
Drug Product Name/ Strength	Atorvaliq (Atorvastatin Calcium)/ 4 mg/mL
Route of Administration	Oral
Applicant Name	CMP Development LLC
Therapeutic Classification/ OND Division	Lipid Altering Agents / CDER/OCHEN/DDLO
RLD/RS Number	NDA-202702 (Lipitor)
Proposed Indication	It is an HMG-CoA reductase inhibitor indicated as an adjunct therapy to diet to reduce the risk of MI, stroke, revascularization and angina in adult patients within CHD, but with multiple risk factors.

Assessment Recommendation: **Adequate**

Assessment Summary:

CMP Development LLC (Applicant) is seeking approval of Atorvastatin Oral Suspension 4 mg/mL (20 mg/5 mL), was originally submitted on 01/13/ 2020 under NDA-213260 via the 505(b)(2) pathway using LIPITOR (atorvastatin calcium) oral tablet 80 mg as the listed drug (LD). The Applicant conducted an in vivo bioequivalence study comparing the listed drug and the proposed drug.

The drug substance (API) is a low solubility compound and belongs to BCS Class II. The Applicant adopted [redacted] (b) (4) (Table 1) [redacted] (b) (4) for Atorvastatin tablets for quality control of the proposed suspension product. Two IRs (dated 07/01/2020 and 08/03/2020) were sent for additional information and clarification. The Applicant's responses are satisfactory (IRs, Responses, and Assessment are detailed under the section "BIOPHARMACEUTICS LIST OF DEFICIENCES"). The proposed quality control dissolution specification (method and criterion) is discriminating towards critical material attributes (CMAs) and critical formulation variables (CFVs) and is found acceptable.

Table 1. Dissolution Method for Atorvastatin Oral Suspension (4mg/mL i.e.,20mg/5mL)

Apparatus	Agitation Speed (rpm)	Dissolution Medium/Temperature	Dissolution Medium Volume (mL)	Dissolution Acceptance Criterion
USP II (Paddle)	75	0.05 M Phosphate buffer, pH 6.8 at 37°C ± 0.5°C	900	NLT [redacted] (b) (4) % (Q) in 15 min
* 20mL of sample suspension of 4mg/mL (equivalent to 80mg drug) is used for dissolution testing which represents highest recommended clinical dose				

List Submissions being assessed (table):

Document(s) Assessed	Date Received
0000 (1): original submission	01/13/2020
0010 (11): Response to IR #1	07/07/2020
0012 (13): Response to IR # 2	08/06/2020

Highlight Key Issues from Last Cycle and Their Resolution: NA

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): None

B.1 BCS DESIGNATION

Assessment:

Solubility: Freely soluble in methanol, slightly soluble in alcohol, very slightly soluble in distilled water, in pH 7.4 phosphate buffer, and in acetonitrile, insoluble in aqueous solutions of pH 4 and below. The Applicant stated that the drug substance belongs to BCS Class II.

Table 2. Solubility in Different Solvents at About 37°C

	Dissolution Media	Solubility (mg /ml)
Saturation solubility at 37°C	Water	0.14
	Phosphate Buffer pH 6.8	0.31
	Acetate Buffer pH 4.5	0.07
	0.1N HCl	0.02 (Degradation)

Permeability: Not provided

Dissolution: API solubility has direct impact on the dissolution of the product. The initial risk is medium.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: ***{Adequate}***

Table 3. Proposed dissolution method and acceptance criterion for quality control of the proposed Atorvastatin Suspension [4mg/mL (20mg/5mL)]

	Apparatus	USP II (paddle)

Dissolution Conditions	Speed of Rotation	75 rpm
	Medium	0.05 M Phosphate buffer, pH 6.8
	Volume	900 mL
	Temperature	37°C ± 0.5°C
Proposed Acceptance Criterion	NLT (b) (4)% (Q) in 15 minutes	

Solubility of Atorvastatin Calcium API was performed in medium with different pHs (Table 4). Based on the solubility data, the pH 6.8 phosphate buffer was selected as its satisfactory with regards to solubility and sink condition. A paddle speed of 75 rpm and medium volume of 900 mL was chosen based FDA database method available for Atorvastatin tablets.

Table 4. Solubility of Atorvastatin Calcium in medium with different pH

The Applicant performed the dissolution studies on two batches (ATOL1111 and ATOL1110) with the same formulation, the same manufacturing process but different API PSD (Table 5) to evaluate discriminating ability of the proposed dissolution method at two different speeds, (b) (4) rpm and 75 rpm. The data indicated that controlling API PSD can reduce the risk on dissolution results and the proposed dissolution method (75 rpm) and acceptance criterion was able to discriminate batch ATOL1111 with large particle size D_{90} = (b) (4) µm (Table 6 Based on results in Table 6 it can be concluded that the proposed dissolution m hod and acceptance criterion is discriminative to CMA i.e., with regards to particle size of atorvastatin in the drug product. It is noted that (b) (4) rpm method provided average dissolution of (b) (4)% dissolution at 15 min for larger particle size batch (ATOL1111, D90 - (b) (4) m); whereas, for the same batch it

was (b) (4)% at 15 min with 75 rpm method.[1] Based on the available data, 75 rpm method is discriminating compared to (b) (4)rpm method. (b) (4) The proposed API supplier specification for PSD is D90 – NMT (b) (4)µm. It is noted that the observed API D90 for drug substance batch (API Supplier batch # - AC1m1640917; Drug product manufacturer batch # - AR17/02764) used for manufacturing of biobatch (VAL/18/0073) is (b) (4)µm.

Table 5. PSD optimization trials on batches ATOL1111 & ATOL1110

Drug product Batch No.		ATOL1111	ATOL1110
API vendor batch No		AC10290513	AC1m0600614
Particle size in µm	D_{10}	(b) (4)	
	D_{50}		
	D_{90}		

Table 6. Dissolution profiles of batches ATOL1111 & ATOL1110

Study parameters		Time points (Min)	% Drug release ATOL1111	% Drug release ATOL1110
USP apparatus	II (Paddle)	5	(b) (4)	
Speed (RPM)	75	10		
Medium	0.05 M, pH 6.8 phosphate buffer	15		
Volume	900 mL	30		
		45		

Further, the Applicant also evaluated the impact of quantitative changes in (b) (4)

(b) (4) . Since volume of suspension (and hence amount of drug) used for dissolution testing may impact dissolution rate and discriminating ability of the method, it was advised that the same procedure that is implemented for biobatch testing and discriminating ability studies should be used for QC dissolution testing. The IR was issued on 07/01/2020[2],

[1] \\CDSESUB1\evsprod\nda213260\0000\m3\32-body-data\32p-drug-prod\atorv-os\32p2-pharm-dev\32p2-3-comp-disso-dev-rep.pdf

[2] \\CDSESUB1\evsprod\nda213260\0008\m1\us\1-2-cover-letters\1-2-2-cover-letters.pdf

the Applicant's response was received on 07/07/2020[3] addressing the deficiencies. The suspension volume of 20mL of 4mg/mL (80mg drug) is used in both dissolution test and quality control consistently. The analytical procedure was updated accordingly (40008-MU-06) (Detailed response is under "BIOPHARMACEUTICS LIST OF DEFICIENCIES"

Further, the Agency sent another IR on 08/03/2020 (b) (4)

[redacted]

Table 7. Comparative dissolution profiles of test and reference products

Dissolution Conditions	Apparatus:	USP-II (Paddle)
	Speed of Rotation:	75 RPM
	Medium:	0.05 M Phosphate buffer, pH 6.8
	Volume:	900 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	NLT (b) (4)% (Q) of the labeled amount of Atorvastatin should dissolve in 15 minutes	
Dissolution Testing Site (Name, Address)	(b) (4)	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours) 5 min	10 min	15 min	30 min	Study Report Location
Study Report # (b) (4)	12-07-18	Reference Product Lipitor® Lot #: W98358 Expiration Date: 02-28-21	80 mg Tablet	12	Mean	(b) (4)				Section 3.2.P.2
					Range					
					%CV					
Study Report # (b) (4)	06-10-19	Test Product Atorvastatin Oral Suspension Lot #: VAL/18/0073/B Manufacture Date: 04-2018	4 mg/mL & Oral Suspension	12	Mean					
					Range					
					%CV					

An update was provided in the CMC team meeting that the OCP's outcome is inadequate since biobatch is not BE to the listed drug and it is recommended by the OCP (1) to

[3] \\CDSESUB1\evsprod\nda213260\0010\m1\us\1-2-cover-letters\1-2-2-cover-letters.pdf
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reformulate the proposed drug product and conduct additional bioavailability studies to demonstrate bioequivalence to the reference listed drug (Lipitor) or (2) to conduct a clinical efficacy study to support the efficacy and safety of the proposed Atorvastatin oral suspension.

Based on data provided, the proposed dissolution method and acceptance criterion (Table 3) of Atorvastatin Suspension 4 mg/mL (20 mg/5 mL) are acceptable.

B.3 CLINICAL RELEVANCE OF DISSOLUTION METHOD & ACCEPTANCE CRITERIA *(e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)*

Assessment: *{Inadequate}*

Two pilot BE studies were performed to evaluating API particle size ATOL1010 (b) (4) µm) and ATOL1032 (b) (4) µm) (Table 8). The batch with larger size of (b) (4) µm failed to meet BE criteria. (Module 2.3.3 of Pharmaceutical Development Report, page 52 – 55). There is a potential of IVIVR, however, the Applicant originally did not submit dissolution profiles of the above pilot study batches. In response to IR # 1, the Applicant provided the requested dissolution data of pilot BE study batches. However, though dissolution profiles of failed pilot BE batches were provided (dated 08/03/2020), it could not be used to evaluate clinical relevance of the dissolution method since as mentioned above, pivotal biobatch is not BE to the listed drug.

Table 8. Comparative results of 90% Confidence Interval – Cmax for two BE study

Study	Particle size	Batch No.	pH	90% Confidence Interval - Cmax	Number of subjects involved
Project 15-007	(b) (4)				
Project: 15-020					

B.12 BRIDGING OF FORMULATIONS

Assessment: *{Adequate}*

In Vitro bridging is not needed as the manufacturing site for commercial is same as the one used for biobatch manufacturing. (Manufacturing site for both the submission and commercial batches of the finished drug product is at (b) (4)

BIOPHARMACEUTICS LIST OF DEFICIENCIES

IR # 1:

1. We note that the amount of drug product sample used in QC dissolution testing procedure (40008-MU-04; Module 3.2.P.5.2) is different from the one used in the report titled, Dissolution profile in different media study report [Module 3.2.P.2]. Clarify the discrepancy in the amount of suspension volume and drug amount used for dissolution testing ((b) (4) . It is recommended that suspension volume used for quality control dissolution testing of commercial batches is the same as the one used in dissolution method discriminating ability studies and dissolution testing of biobatch and registration batches. As necessary, provide updated analytical procedure for dissolution testing procedure.

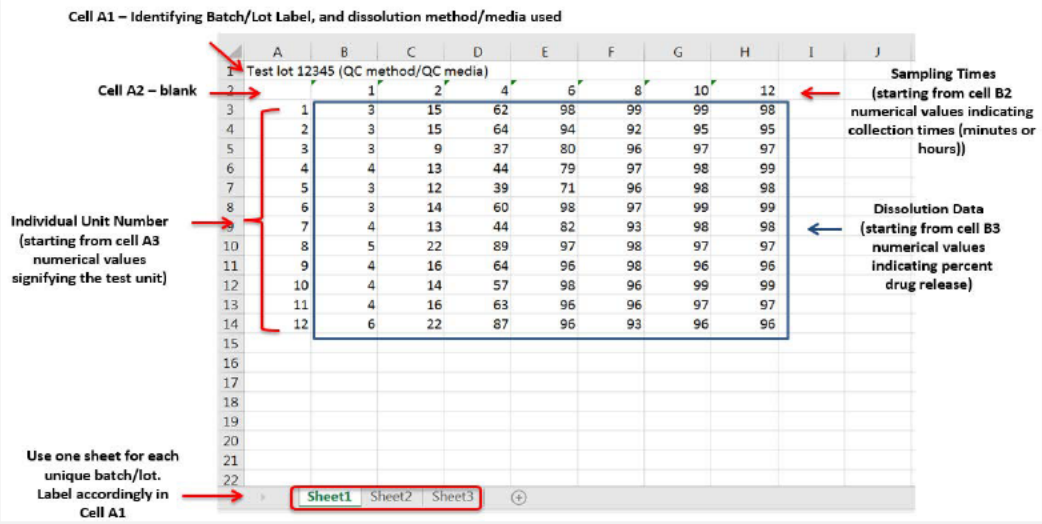
Applicant's Response

In response to this IR, the Applicant stated that for biobatch (VAL/18/0073/B) and multimedia dissolution testing, suspension volume of 20mL of 4mg/mL (80mg drug) was used for dissolution testing. Two exhibit/registration batches (VAL/18/0074/A and VAL/18/0075/A) that was tested with (b) (4) were retested with 20mL (80mg drug) for dissolution and respective profile data are provided.
Also, the Applicant revised quality control (QC) dissolution analytical procedure and provided method validation report in Section 3.2.P.5.2[6] and Section 3.2.P.5.3[7], respectively.

2. For further evaluation of the proposed QC dissolution method for your product, provide dissolution profiles of the two pilot BE study batches ATOL1010 (API PSD - D90 of (b) (4) µm) and ATOL1032 (API PSD – D90 of (b) (4) µm) generated using the proposed quality control dissolution method. In addition, also provide, dissolution profiles of registration batches VAL/18/0074/A, and VAL/18/0075/A. Provide manufacturing dates, dissolution testing dates, and age of these products used for testing. Provide dissolution profiles of the above batches including biobatch VAL/18/0073/B in the following excel format in M 3.2.P.5.4.

Example- Reporting of individual vessel dissolution data

[6] \\cdsesub1\evsprod\nda213260\0010\m3\32-body-data\32p-drug-prod\atorv-os\32p5-contr-drug-prod\32p52-analyt-proc\32p52-1-analyt-proc.pdf
[7] \\cdsesub1\evsprod\nda213260\0010\m3\32-body-data\32p-drug-prod\atorv-os\32p5-contr-drug-prod\32p53-val-analyt-proc\32p53-1-val-analyt-proc-rep.pdf



Follow the instructions provided in "Specifications for File Format Types Using eCTD Specifications".

Applicant's Response

Dissolution data for batches ATOL1010 (API PSD - D90 of (b) (4) µm), ATOL1032 (API PSD – D90 of (b) (4) µm,) VAL/18/0074/A, VAL/18/0075/A and the manufacturing dates, dissolution analysis and age of batches at dates of dissolution testing were reported in the excel sheets [8]

Reviewer's Assessment: The Applicant's response is acceptable.

1. The amount of drug product used for biobatch and in multiple media dissolution testing have been edited as FDA's recommendation (80 mg drug per test). Analytical procedure is updated accordingly.
2. Dissolution data for requested batches were provided following FDA's template.

IR # 2:

In dissolution analytical procedure (40008-MU-06), it is unclear (b) (4) *. Update your analytical procedure accordingly.*

Applicant's Response:

[8] \\cdsesub1\evsprod\nda213260\0010\m3\32-body-data\32p-drug-prod\atorv-os\32p5-contr-drug-prod\32p54-batch-analys\32p54-disso-prof.xlsx

Reviewer's Assessment: The Applicant's response is acceptable.
Each bottle contains multiple doses; therefore, it is acceptable to use 6 samples from the same suspension bottle for quality control dissolution testing.

Primary Biopharmaceutics Assessor's Name and Date: Huong Moldthan, Ph.D.
9/28/2020

Secondary Assessor Name and Date (and Secondary Summary, as needed): Poonam Delvadia, Ph.D.
09/28/2020

Huong Moldthan

Digitally signed by Huong Moldthan
Date: 9/28/2020 12:52:15PM
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Poonam Delvadia

Digitally signed by Poonam Delvadia
Date: 9/28/2020 12:54:38PM
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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MUTHUKUMAR RAMASWAMY
10/05/2020 08:05:20 PM