CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214439Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 214439 Resubmission

NORLIQVA (Amlodipine) Oral Solution

OPQ Integrated Quality Review

Recommendation: Approval

Drug Name/Dosage Form	NORLIQVA (amlodipine) oral solution
Strength	1.0 mg/mL of amlodipine (equivalent to 1.385 mg of amlodipine besylate)
Route of Administration	Oral solution
Indication	Indicated for the treatment of hypertension and chronic stable angina
Rx/OTC Dispensed	Rx
Applicant	CMP Development LLC
Submissions (s) Reviewed	NDA 214439 and all submitted CMC amendments

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Ben Zhang	OPQ/ONDP/DNDAPI/NDB3
Drug Product, Labeling, and Environmental Assessment	Akm Khairuzzaman	OPQ/ONDP/DNDPIII/NDPB5
Process and Facility	Upasana Sahu	OPQ/OPMA/DPMAIII/PMB7
Biopharmaceutics	N/A	N/A
Microbiology	Eric Adeeku	OPQ/OPMA/DMAI/MAB1
Regulatory Business Process Manager	Grafton Adams	OPQ/OPRO/DRBPMI/RBPMB2
Application Technical Lead	Theodore Carver	OPQ/ONDP/DNDPIII/NDPB5

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Office of Pharmaceutical Quality Review team has assessed NDA 214439 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 it purports to have. As such, OPQ recommends approval of this NDA from a quality perspective.

B. Recommendation on Post-Marketing Commitments (PMCs), Agreements, and/or Risk Management Steps, if Applicable

Not applicable.

II. Quality Assessment Summary

A. Background: The Applicant, CMP Development LLC, seeks U.S. marketing approval for NORLIQVA (amlodipine) under the provisions of Sectin 505(b)(2) od the Federal Food, Drug, and Cosmetics Act. The submission relies on the FDA's previous findings of safety and effectiveness for the Listed Drug (LD) Norvasc® (amlodipine) tablets (NDA 019787, approved July 31, 1992), and in-vivo bioavailability studies. Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle and is indicated for treatment of hypertension and chronic stable angina. The amlodipine oral suspension was developed for administration to patients with difficulty swallowing (dysphagia). In the previous integrated quality assessment of this NDA, it was not deemed approvable due to deficiencies in two manufacturing facilities (b) (4) (b) (4). The quality assessment of this resubmission of NDA 214439 included reviews of the drug substance, drug product, quality labeling, and manufacturing and facilities.

B. Drug Substance (Amlodipine Besylate, USP)**:** Dr. Ben Zhang reviewed the drug substance information and found it to be adequate. In the last review cycle, there were no unresolved deficiencies for the drug substance. In the current resubmission, the Applicant submitted updates to analytical procedures and verification information, and Dr. Zhang reviewed these and found them to be adequate. The NDA references DMF (b) (4) for CMC information for (b) (4) A new amendment to this DMF was submitted since the last review, and Dr. Zhang reviewed this amendment and found that the DMF remains adequate to support manufacturing of the drug substance. The drug substance retest period is (b) (4) months when stored according to the manufacturer's stated storage conditions.

C. Drug Product (Amlodipine Oral Solution): Dr. Akm Khairuzzaman reviewed the drug product information and found it to be adequate. In the current resubmission, the only new

information for the drug product concerned testing for [redacted] these analytical procedures were transferred to a new facility. Dr. Khairuzzaman reviewed these procedures and found them to be adequate. The drug product information remains adequate to support approval.

C.1. Manufacturing: Dr. Upasana Sahu conducted the review of the NDA with respect to the drug product manufacturing process and controls and found that this information remains adequate. The drug manufacturing process includes the following steps: [redacted] In the previous review, an additional comment to the Applicant requested that the Applicant [redacted] which were found to be adequately supported by data provided by the Applicant. Overall, the description of the commercial process, controls, unit operations, and incoming materials were found to be adequate.

C.2. Microbiological Aspects: Dr. Eric Adeeku conducted the microbiology review, and, since the Applicant submitted no new information related to microbiology, conclude that the NDA remains adequate from the microbiology perspective without need for further review, including antimicrobial validation and testing.

C.3. Biopharmaceutics Aspects: Since the drug product is an oral solution, a biopharmaceutics review is not applicable for this submission.

III. Stability, Storage Conditions and Expiration Date

Dr. Akm Khairuzzaman reviewed the long-term stability studies and other supporting information for the drug product. The stability data remain adequate to support an expiration period of 24 months for the proposed product when stored at 20°C to 25°C (68°F to 77°F) in the commercial packaging. Excursions can be permitted to 15°C to 30°C (59°F to 86°F).

IV. Quality Labeling

Dr. Akm Khairuzzaman reviewed the product quality labeling and found it to be acceptable. Final revisions to the labeling included revising the non-proprietary name in the prescribing information to conform to the container/closure labeling (amlodipine) instead of amlodipine [redacted], which is accordance with FDA policy with respect to naming of active moieties, for this dosage form. This decision was discussed with DMEPA prior to the final recommendation.

V. Assessment of Manufacturing Facilities

Dr. Upasana Sahu conducted the review of the manufacturing facilities. The previous review of NDA 214439 concluded that NDA 214439 could not be approved until deficiencies in two facilities, [redacted], were corrected. The Applicant withdrew [redacted], a drug substance testing facility, and

transferred its responsibilities to [redacted] (b) (4) which were found to be in compliance and adequate to conduct this testing.
The drug product manufacturing facility, [redacted] (b) (4) was deemed high risk because the facility has never been inspected before by FDA, and a previous 704(a)(4) records review by FDA identified cGMP deficiencies. After review of the firm's responses to deficiencies identified by FDA, FDA determined that a preapproval inspection of this facility was necessary to support approval. An on-site pre-approval inspection (PAI) was conducted from 1/27/2022 to 02/02/2022. The inspection was classified as VAI, and the facility was approved based on this PAI and the district office recommendation. The manufacturing review concluded that all facilities are adequate to support approval of this NDA. For the tabulated status of all facilities, see the Facilities Table provided on page 3 of the Manufacturing Integrated Assessment.

VI. Environmental Assessment

The applicant's claim of categorical exclusion from the environmental assessment requirements, under 21 CFR 314.50 (d) (l) (iii), remains acceptable.

VII. Life Cycle Knowledge Information Not applicable

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead (ATL) Assessment and Signature:

At present, there are no outstanding deficiencies related to the drug substance, drug product, microbiology, manufacturing, and environmental assessment sections of this NDA. The OPQ overall recommendation for NDA 214439 is approval.

Theodore Carver, Ph.D.
Senior Product Quality Assessor, OPQ/ONDP/DNDPIII/NDPB5

Theodore Carver

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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	(b) (4) ® (amlodipine (b) (4) oral solution)	Acceptable
Established name(s)	Amlodipine Oral Solution, 1 mg/mL	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.	Oral solution, 1 mg/ml	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.	N/A	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 solution	Acceptable
Strength(s) in metric system	Not applicable	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Follows the USP Salt Policy per FDA Guidance.	Acceptable.

1.2.3 Section 11 (DESCRIPTION)

Items	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	(b) (4) ® (amlodipine (b) (4) oral solution)	Acceptable
Dosage form(s) and route(s) of administration	Solution, oral	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Follows approved USP product for the LD.	Acceptable
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Provided	Acceptable
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.	N/A	Acceptable
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	The following statement is on bottle labeling: "Contains 4% v/v alcohol"	Acceptable
Statement of being sterile (if applicable)	N/A	Acceptable
Pharmacological/ therapeutic class	Provided	Acceptable
Chemical name, structural formula, molecular weight	Yes	Acceptable
If radioactive, statement of important nuclear characteristics.	Not Applicable	Acceptable
Other important chemical or physical properties (such as pKa or pH)	Solubility and physical description of the active ingredient is provided	Acceptable
Remove statements that may be misleading or promotional (e.g.,	None present	Acceptable

“synthesized and developed by Drug Company X,” “structurally unique molecular entity		

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 solution	Acceptable
Strength(s) in metric system	Not applicable	Acceptable
Available units (e.g., bottles of 100 tablets)	Supplied in 150 mL Amber Glass Bottles with (b) (4) Child Resistant Closures	Acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Provided in section 3 as follows: pale straw-colored solution with a peppermint flavor	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.	N/A	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° to 25°C (68° to 77°F)], excursions permitted to 15° to 30°C (59° to 86°F)	Acceptable

Include information about child-resistant packaging	Supplied in 150 mL Amber Glass Bottles with (b) (4) Child Resistant Closures	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., 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): Not applicable

3.0 CARTON AND CONTAINER LABELING

3.1 Bottle Label

(b) (4)

3.2 Outer package: The product will not be packaged in any secondary package.

Items	Information Provided in the NDA	Assessor's Comments
Proprietary name, established name, and dosage form (font size and prominence)	(b) (4) ® (amlodipine (b) (4) oral solution)	Acceptable
Dosage strength	1 mg/ml	Acceptable
Route of administration	Oral solution	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	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 room temperature [20° to 25°C (68° to 77°F)]	Acceptable
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single patient-use)	N/A	Acceptable
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	Acceptable
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Provided	Acceptable
Name of manufacturer/distributor	Distributed by CMP Pharma, Inc., Farmville, NC 27828	Acceptable

Medication Guide	Not Applicable	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.	Follows approved USP product for the LD.	Acceptable

Assessment of Carton and Container Labeling: *Adequate*

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation: **Adequate**

Primary Drug Product Assessor Name and Date: Akm Khairuzzaman, Ph.D., 1/20/2022.
Secondary Assessor Name and Date (and Secondary Summary, as needed): Theodore Carver, Ph.D., 1/20/2022.

Akm Khairuzzaman

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NDA 214439: (b) (4) (Amlodipine) Oral Solution

OPQ's Integrated Quality Review

Recommendation: A Complete Response

Drug Name/Dosage Form	(b) (4) (amlodipine) oral solution
Strength	1.0 mg/mL of amlodipine (equivalent to 1.385 mg of amlodipine besylate)
Route of Administration	Oral solution
Indication	Indicated for the treatment of hypertension and chronic stable angina
Rx/OTC Dispensed	Rx
Applicant	CMP Development LLC
Submissions (s) Reviewed	NDA 214439, IND # 141056, and all submitted CMC amendments

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Ben Zhang	OPQ/ONDP/DNDAPI/NDB3
Drug Product, Labeling, Environmental Assessment	Akm Khairuzzaman	OPQ/ONDP/DNDPIII/NDPB5
Process and Facility	Upasana Sahu	OPQ/OPMA/DPMAIV/PMB12
Biopharmaceutics	N/A	
Microbiology	Eric Adeeku	OPQ/OPMA/DMAI/MAB1
Application Technical Lead (ATL)	Mohan Sapru	OPQ/ONDP/DNDPIII/NDPB5

Regulatory Business Process Manager: Grafton Adams; OPQ/OPRO/DRBPMI/RBPMB2

Related/Supporting Documents:

Document	Application Number	Description
DMF	Type II DMF# (b) (4)	Previously reviewed and found adequate

CONSULTS:
None.

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Based on integrated quality review by the Office of Pharmaceutical Quality (OPQ), manufacturing facilities-related deficiencies remain currently unresolved because of a) an official action indicated (OAI) classification for the drug the drug substance testing facility, (b) (4) and b) a 704(a)(4) review of (b) (4) has identified currently unresolved CGMP deficiencies, resulting in 'withhold' recommendation for the facility. Therefore, from an OPQ perspective, this NDA is not deemed ready for approval in its present form until the above-mentioned deficiencies are satisfactorily resolved. As such, OPQ recommends a Complete Response (CR) action from a product quality perspective.

B. Recommendation on Post-Marketing Commitments (PMCs), Agreements, and/or Risk Management Steps, if Applicable

Not applicable.

II. Background, and Quality Assessment Summary

The Applicant, CMP Development LLC, has sought U.S. marketing approval for (b) (4) (amlodipine) Oral Solution under the provisions of Section 505(b)(2) of the Federal Food and Cosmetic Act. The submission relies on a) the FDA's previous findings of safety and effectiveness for the Listed Drug (LD) Norvasc® (amlodipine) tablets (NDA 019787, approved July 31, 1992), and b) *in-vivo* bioavailability studies. The amlodipine oral suspension is a 'convenience dosage form' developed for patients with dysphagia (difficulty swallowing). Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle.

A. Drug Substance (Amlodipine Besylate, USP) Quality Summary

The drug substance Amlodipine Besylate, USP is a white crystalline powder, and is classified as a BCS Class I compound; exhibiting high solubility. For CMC details concerning the drug substance, the Applicant has cross-referenced Type II DMF (b) (4), which along with DMF amendments have been previously reviewed and found to be adequate. Quality attributes of the drug substance such as polymorphism and particle size distribution are not critical for the oral solution dosage form and do not require controls. The drug substance, which has one chiral center (i.e., 2 enantiomers), is a racemic mixture. Based on information provided in the NDA, the drug substance release specification includes testing the critical quality attributes

(CQAs) and conforms to USP monograph. The retest period is (b) (4) months when stored according to the manufacturer's stated storage conditions.

B. Drug Product (Amlodipine Oral Solution) Quality Summary

B.1. Product Design, and Release Specification:

Pharmaceutical development studies adequately support the formulation design, including excipient selection and excipient levels. No novel or human/animal-origin excipients are used in the formulation. Specifically, the drug product contains the drug substance and inactive ingredients namely; Maltitol, Butylated Hydroxyanisole, Ethanol (b) (4), Glycerin, and (b) (4) Peppermint Flavor (b) (4). All excipient/inactive ingredients are USP/NF compendial designated and are controlled through their monograph-recommended specification. The maximum daily dose (MDD) is 10 mg, which is equivalent to 10 mL of Amlodipine Oral Solution. The quantities of excipients used in the test formulation have been justified either because these are present in the formulation below the IIG limits, or do not exceed the acceptable limits for FDA-approved drug products for oral route, or a relevant safety assessment has been provided. The proposed product Amlodipine Oral Solution, 1 mg/mL, which is also intended to be dosed in children population (at or above 6-year-old), is packaged in 150 mL Amber (b) (4) glass bottles with (b) (4) child-resistant closures. The proposed container closure system is appropriate for the intended use. The level of alcohol used is reasonable for pediatric patient population (age 6 years or older) based on other FDA-approved products and FDA's inactive ingredient database.

The product release specification, involving testing of all the product critical quality attributes (CQAs), is adequate to ensure the consistent product quality. The revised limit of NLT (b) (4) and NLT (b) (4) (b) (4), respectively, are acceptable. The proposed limit of NMT (b) (4) (b) (4), is adequately justified. The non-compendial analytical procedures used for testing the drug product have been validated according to ICH guidelines. A risk assessment regarding levels of elemental impurities in the drug product (from all possible sources of elemental impurities such as the drug substance, excipients and manufacturing equipment) have been assessed in accordance with the *ICH guideline Q3D and USP General Chapters <232> and <233>*. Based on this assessment, the elemental impurities in the proposed product do not exceed the ICH Q3D-compliant permitted daily exposure (PDE) limits. Hence, no release testing for elemental impurities is required. In conclusion, the product design, selection of excipients and control of product quality via release testing are adequate.

B.2. Manufacturing: Briefly, the product manufacturing includes (b) (4) The commercial batch formula for the oral (b) (4) suspension reflects the proposed composition and is consistent with the commercial batch record. Adequate information has been provided about incoming materials, and

unit operations. The in-process controls, including the revised in-process control [redacted] are adequate. [redacted] The product has been shown to be compatible with 40-micron polypropylene filters for up to 48 hrs. Overall, the manufacturing process is well-controlled.

B.3. Microbiological Aspects: [redacted] Adequate antimicrobial validation data, per USP <51>, have been provided to support the minimum release and stability specification for the [redacted] The product release specification includes microbial testing per USP <61> and USP <62>. The container closure system is designed to maintain the microbiological quality of the product.

B.4. Biopharmaceutics Aspects: Since the drug product is an oral solution, a biopharmaceutics review is not applicable for this submission.

B.5. Stability, Storage Conditions and Expiration Date: The stability data support an expiration period of 24 months for the proposed product when stored at 20°C to 25°C (68°F to 77°F) in the commercial packaging. Excursions can be permitted to 15°C to 30°C (59°F to 86°F).

C. Assessment of Manufacturing Facilities

The drug product manufacturing facility, [redacted], is deemed high risk because the facility has never been inspected before by FDA. A 704(a)(4) records review was conducted for this facility for an earlier non-sterile oral solution application, where the drug product was manufactured [redacted] in the same facility. The 704(a)(4) review identified CGMP deficiencies, including deficient records of process parameters and in-process controls for certain unit operations. The firm's responses to 704(a)(4) deficiencies have been reviewed but critical outstanding concerns remain unresolved. Thus, the identified deficiencies are currently unresolved, resulting in 'withhold' recommendation for [redacted] In addition, the drug substance testing facility, [redacted] is currently under the OAI. As a result, the facility remains out of compliance at this time and outstanding CGMP concerns preclude recommending the facility to be acceptable to support the drug substance testing role for this NDA. In summary, based on above-specified currently unresolved facilities-related deficiencies, from a product quality perspective, a complete response is recommended for this NDA.

D. Environmental Assessment

The applicant's claim of categorical exclusion from the environmental assessment requirements, under 21 CFR 314.50 (d) (l) (iii), is deemed acceptable.

E. List of Outstanding Facility Deficiencies

Facility Inspections:

1. During a review of records requested under section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act, and provided by (b) (4) manufacturing facility, the FDA noted objectionable conditions. 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. The FDA will communicate the outstanding issues to the facility no later than 10 business days from issuing this complete response letter. Please contact (b) (4) manufacturing facility for additional information. An inspection of the (b) (4) (b) (4) facility is required before the application can be approved. FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP. Due to restrictions on travel, we are unable to conduct an inspection of the (b) (4) (b) (4) facility prior to the User Fee Date. We will continue 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/emergencypreparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidancedocuments-industry-fda-staff-and-other-stakeholders.*

2. During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

Additional Comment:

We acknowledge you added the (b) (4) testing as part of the (b) (4) for commercial production. You stated in Section 3.2.P.3.4 that the acceptance criteria (b) (4) (b) (4) will be established based on results from first three commercial batches. We remind you that process validation is to confirm the process design and demonstrate that the commercial manufacturing process performs as expected *(Guidance for Industry Process Validation: General Principles and Practices (2011)*, rather than to develop and/or finalize the commercial manufacturing process and define the acceptance criteria based on the data obtained from the process validation. Therefore, provide the acceptance criteria (b) (4) based on data collected from the manufacturing of development and registration batches and demonstrate that scalability issues for all scale-dependent parameters have been taken into account.

Final Risk Assessment

NDA 214439: (b) (4) (Amlodipine) Oral Solution

Attribute/ CQA	Factors Impacting CQAs	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations
Assay, Stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment/site	Low (L)	(b) (4)	Acceptable	
Physical Stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/ equipment/ site	Low (L)		Acceptable	N/A

Attribute/ CQA	Factors Impacting CQAs	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations
Physical Stability (phase separation)	• Formulation • Raw materials • Process parameters • Scale/ equipment/ site	Low (L)	(b) (4)	Acceptable	Any proposed changes to formulation, manufacturing or the control strategies will need to be evaluated for possible impact on product CQAs
Dosing Accuracy	• Formulation • Dosing device • Process parameters • Scale/equipment/site	Low (L)		Acceptable	N/A
Palatability	• Formulation • Excipient change • Process parameters Scale/equipment/site	Moderate (M)		Acceptable	N/A
Leachables	• Formulation • Container closure • Process parameters Scale/equipment/site	Moderate (M)		Acceptable	N/A

Attribute/ CQA	Factors Impacting CQAs	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations
Microbial limits	• Formulation • Raw materials • Process parameters Scale/equipment/site	Low (L)	(b) (4)	Acceptable	N/A

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead (ATL) Assessment and Signature

Based on integrated quality review by the Office of Pharmaceutical Quality (OPQ), manufacturing facilities-related deficiencies remain currently unresolved because of a) an official action indicated (OAI) classification for the drug the drug substance testing facility, (b) (4) and b) a 704(a)(4) review of (b) (4) (b) (4) has identified currently unresolved CGMP deficiencies, resulting in 'withhold' recommendation for the facility. Therefore, from an OPQ perspective, this NDA is not deemed ready for approval in its present form until the above-mentioned deficiencies are satisfactorily resolved. As such, OPQ recommends a Complete Response (CR) action from a product quality perspective.

Mohan Sapru, M.S., Ph.D.
Application Technical Lead (ATL)
CMC Lead; Division of Cardiology and Nephrology (DCN)
OPQ/ONDP/DNDPIII/NDPB5

Mohan K. Sapru -S

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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	(b) (4)® (amlodipine (b) (4) oral solution)	Acceptable
Established name(s)	Amlodipine Oral Solution, 1 mg/mL	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.	Oral solution, 1 mg/ml	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.	N/A	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 solution	Acceptable
Strength(s) in metric system	Not applicable	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Follows the USP Salt Policy per FDA Guidance. Additionally, FDA recommended to	Acceptable after the applicant make the recommended changes on the label

	add equivalence statement of "(equivalent to 1.385 mg of Amlodipine Besilate per ml)" in section 11.	

1.2.3 Section 11 (DESCRIPTION)

Items	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	(b) (4) ® (amlodipine (b) (4) oral solution)	Acceptable
Dosage form(s) and route(s) of administration	Solution, oral	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Follows approved USP product for the LD.	Acceptable
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Provided	Acceptable
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.	N/A	Acceptable
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Not Provided	Not Acceptable
Statement of being sterile (if applicable)	N/A	Acceptable
Pharmacological/ therapeutic class	Provided	Acceptable
Chemical name, structural formula, molecular weight	Yes	Acceptable
If radioactive, statement of important nuclear characteristics.	Not Applicable	Acceptable

Other important chemical or physical properties (such as pKa or pH)	Solubility and physical description of the active ingredient is provided	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 solution	Acceptable
Strength(s) in metric system	Not applicable	Acceptable
Available units (e.g., bottles of 100 tablets)	Supplied in 150 mL Amber Glass Bottles with (b) (4) Child Resistant Closures	Acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Provided in section 3 as follows: pale straw-colored solution with a peppermint flavor	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.	N/A	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	None	Acceptable

maintain stability, etc.)		
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at room temperature [20° to 25°C (68° to 77°F)], excursions permitted to 15° to 30°C (59° to 86°F)	Acceptable
Include information about child-resistant packaging	Supplied in 150 mL Amber Glass Bottles with (b) (4) Child Resistant Closures	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., 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): Not applicable

3.0 CARTON AND CONTAINER LABELING

3.1 Bottle Label

(b) (4)

3.2 Outer package

Not provided

Reviewer's note: Applicant will be asked to provide outer package labeling

Items	Information Provided in the NDA	Assessor's Comments
Proprietary name, established name, and dosage form (font size and prominence	(b) (4)® (amlodipine (b) (4) oral solution)	Acceptable
Dosage strength	1 mg/ml	Acceptable
Route of administration	Oral solution	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	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 room temperature [20° to 25°C (68° to 77°F)]	Acceptable
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single patient-use)	N/A	Acceptable
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion"	N/A	Acceptable

statement.		
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Not provided on labeling	Not acceptable
Name of manufacturer/distributor	Distributed by CMP Pharma, Inc., Farmville, NC 27828	Acceptable
Medication Guide	Not Applicable	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.	Follows approved USP product for the LD.	Acceptable

Assessment of Carton and Container Labeling: *Inadequate*

ITEMS FOR ADDITIONAL ASSESSMENT

1. In section 11, the FDA suggests including equivalence statement, "equivalent to 1.385 mg of Amlodipine Besilate per ml"
2. Provide outer package labeling information
3. Provide the amount of alcohol present in terms of percent volume of absolute alcohol on your labeling.

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

Primary Drug Product Assessor Name and Date: Akm Khairuzzaman, Ph.D., 2/19/2021.
Secondary Assessor Name and Date (and Secondary Summary, as needed): David Claffey, Ph.D., 2/19/2021.

Akm Khairuzzaman

Digitally signed by Akm Khairuzzaman
Date: 2/22/2021 02:22:37PM
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David Claffey

Digitally signed by David Claffey
Date: 2/22/2021 03:21:04PM
GUID: 508da71e00029e20b201195abff380c2

Comments: will follow up with alcohol content statement in labeling, the use of [redacted] (b) (4) in established name and the possible expression of the strength [redacted] (b) (4)

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CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	214439
Assessment Cycle Number	01
Drug Product Name/ Strength	(b) (4) (Amlodipine oral solution, 1 mg/mL)
Route of Administration	Oral
Sponsor Name	CMP Development LLC.
Therapeutic Classification/ OND Division	Calcium channel blocker / N/A
Manufacturing Site	(b) (4)
Method of Sterilization	Non-sterile

Assessment Recommendation: **Adequate**

Assessment Summary: The submission is **recommended** for approval.

Document(s) Assessed	Date Received
1 (eCTD sequence 0000)	06/22/2020

List Submissions being assessed:

Submit	Received	Review Request	Assigned to Reviewer
06/22/2020	06/22/2020	N/A	07/09/2020

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks:

This is an electronic submission.
Goal date is 04/22/2021.
No comparability protocols are included in this NDA.

Concise Description of Outstanding Issues: None

Supporting Documents: None

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Description of drug product –

(section 3.2.P.1).
Amlodipine Oral Solution, 1 mg/mL is a calcium channel blocker and may be used alone or in combination with other antihypertensive and antianginal agents for the treatment of hypertension and coronary artery disease.

Drug product composition –

(section 3.2.P.1.2).

Ingredient	Function	Quantity/mL (mg/mL)
Amlodipine, USP (Amlodipine besilate)[1]	API	1.00 mg ~ 1.385 mg of Amlodipine besilate
Maltitol, NF (b) (4)	(b) (4)	
Butylated hydroxyanisole, (b) (4)		
Ethanol, (b) (4)		
(b) (4) Peppermint Flavor (b) (4)		
Glycerin, USP		

(b) (4)

Description of container closure system –

(sections 3.2.P.1 and 3.2.P.7).

Amlodipine Oral Solution, 1 mg/mL is packaged in 150 mL Amber (b) (4) (b) (4) Glass Bottles with a (b) (4) Child Resistant Closures and is designed to protect the product (b) (4) (b) (4) under ordinary conditions of handling, shipping, storage, and distribution.

Component	Description	Manufacturer
Container	150 mL Amber (b) (4) Glass (b) (4) Bottles	(b) (4)
Closure	(b) (4) Child Resistant Closures	

The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain the microbiological quality of the product.

Adequate

(b) (4)

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(b) (4)

Adequate

R REGIONAL INFORMATION

Executed Batch Records

(section 3.2.R).

Executed lot #(s):

- VAL/18/0090
- VAL/18/0091
- VAL/18/0092

The batch records provide the description of the manufacturing processes (b) (4).

Adequate

Comparability Protocols

No comparability protocols are included in this NDA.

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

Post-Approval Commitments

None

Adequate

MICROBIOLOGY LIST OF DEFICIENCIES: None

Primary Microbiology Assessor Name and Date:

Eric Adeeku, Ph.D., 09/22/2020

Secondary Assessor Name and Date

Jesse Wells, Ph.D., 09/22/2020

Eric Adeeku

Digitally signed by Eric Adeeku
Date: 9/23/2020 09:58:40AM
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Jesse Wells

Digitally signed by Jesse Wells
Date: 9/23/2020 09:23:57AM
GUID: 508da70b00028ea901ac6652677f7d00

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/s/

MOHAN K SAPRU
03/27/2021 12:10:57 AM