

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

214952Orig1s000

PRODUCT QUALITY REVIEW(S)



Template Revision: 03

Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	5		



NDA Executive Summary

1. Application/Product Information

NDA Number.	214952		
Applicant Name	CMP Development LLC		
Drug Product Name	LIQREV (sildenafil) oral suspension		
Dosage Form.	Suspension		
Proposed Strength(s)	10 mg/mL		
Route of Administration	Oral		
Maximum Daily Dose	60 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Treatment of pulmonary arterial hypertension (PAH) (WHO Group I) in adults to improve exercise ability and delay clinical worsening.		
Drug Product Description	White to off-white opaque suspension with a strawberry flavor.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	20°C to 25°C		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Zhengfu Wang OPQ/ONDP/DNDAPI/NDB3	N/A
	<i>Drug Product/ Labeling</i>	Ali Mohamadi OPQ/ONDP/DNDPIII/NDPB5	Theodore Carver OPQ/ONDP/DNDPIII/NDPB5



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	<i>Manufacturing</i>	Carl Lee OPQ/OPMA/DPMAIV/PMB12	Vidya Pai OPQ/OPMA/DPMAIV/PMB12
	<i>Biopharmaceutics</i>	Not applicable (see previous reviews)	
	<i>Microbiology</i>	Not applicable (see previous reviews)	
	<i>Other (specify):</i>	N/A	
	<i>RBPM</i>	Grafton Adams OPQ/OPRO/DRBPMI/RBPMB2	
	<i>ATL</i>	Theodore Carver OPQ/ONDP/DNDPIII/NDPB5	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

An expiry dating period of 24 months is granted for the drug product stored at 20°C to 25°C (68°F to 77°F) with 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.) Background:

The Applicant, CMP Development LLC, seeks U.S. marketing approval for LIQREV (Sildenafil) Oral Suspension 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) REVATIO (sildenafil) tablet, previously approved under NDA 021845, and b) in-vivo bioavailability studies. Sildenafil is a phosphodiesterase-5 (PDE-5) inhibitor indicated for the treatment of



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pulmonary arterial hypertension in adults, to improve exercise ability and delay clinical worsening. The CMC review of the previous submission concluded that the NDA was not approvable due to GMP deficiencies identified in the drug substance manufacturing facility (See IQA review of NDA SD 18, dated April 11, 2022). In the NDA amendment (SD 22) currently under review, the Applicant has added an alternate drug substance manufacturer (b) (4). This Integrated Quality Assessment includes reviews of the drug substance, drug product, and manufacturing aspects of the sildenafil oral suspension.

2.) Drug Substance (sildenafil citrate):

The drug substance, sildenafil citrate USP, is a white to off-white hygroscopic crystalline powder, with a specification that conforms to the USP monograph and includes appropriate tests for critical quality attributes to ensure drug product quality including particle size distribution. The Drug Master File (DMF) containing drug substance CMC information for the alternate drug substance manufacturer (DMF (b) (4) Holder: (b) (4) (b) (4)) was last reviewed and found adequate in July 2022. The drug substance review concluded that this DMF is adequate for supporting the alternate drug substance. The NDA resubmission provided data to support the comparability of one lot of drug product manufactured using drug substance from the new drug substance supplier (b) (4) (b) (4) (see also drug product and manufacturing reviews). In addition, new information including a risk assessment for (b) (4) impurities was reviewed for the NDA resubmission. The drug product manufacturer has set a retest period of (b) (4) from the date of drug substance batch release for batches of the sildenafil citrate drug substance.

3.) Drug Product (sildenafil oral solution):

The drug product is a new liquid oral suspension formulation of sildenafil containing sildenafil citrate and compendial excipients including sodium benzoate, a (b) (4). The CMC information for the drug product was previously reviewed and found to be adequate, and the current review of the NDA resubmission (SD 22) and amendments includes assessment of impurities and leachables. The risk assessments for elemental impurities, potential (b) (4) impurities, (b) (4) and leachables were found to be adequate. The drug product review concluded that the tests and acceptance criteria in the drug product specification are adequate to support the quality of the sildenafil suspension drug product. The specification included tests for resuspendability, sedimentation volume, and particle size to evaluate critical quality attributes of the oral



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suspension. Long-term and accelerated stability data for three primary drug product batches manufactured at (b) (4) L scale support a shelf life of 24 months for the drug product stored at 20°C to 25°C (68°F to 77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F). Stability data support an in-use period of 90 days after the bottle is opened.

4.) Manufacturing:

Process: The manufacturing process involves (b) (4)

(b) (4) The manufacturing process was found to be adequate in previous reviews. There have been no changes to the manufacturing process for the drug product in the current submission (SD 22), and it remains adequate.

Facilities: In the previous review of this NDA (See Integrated Quality Assessment of the NDA resubmission SD 18, dated April 11, 2022), the drug substance manufacturer, (b) (4) (FEI: (b) (4)), was in OAI status due to GMP deficiencies. The Applicant has included the original drug substance manufacturer and an alternate manufacturer, (b) (4) (FEI (b) (4) in this NDA resubmission. Both drug substance manufacturers are recommended for approval based on previous histories including recent facility inspections with satisfactory outcomes. All other manufacturing facilities remain GMP compliant and the overall recommendation for all manufacturing facilities is approval for this NDA. See page 3 of the manufacturing assessment for the status and basis for approval of each facility.

5.) Quality Labeling:

The quality labeling was reviewed and found to be adequate pending recommended changes, and final revisions to the labeling are ongoing.

6.) Other Disciplines:

For the reviews by the biopharmaceutics and microbiology review teams, see previous IQAs and reviews of NDA 214952. Since there was no change in the CMC information submitted in the NDA 214952 resubmission (SD 22) with respect to these disciplines, the CMC information remains adequate for each.

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



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Recommendation by Subdiscipline:

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

Environmental Assessment: Categorical Exclusion - Adequate

QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comments:

Comparability Protocols (PACMP): No

Comments:

Additional Lifecycle Comments: None.



Theodore
Carver

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name ¹	Adequate	LIQREV® (sildenafil) oral suspension
Route(s) of administration	Adequate	oral suspension
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	Oral Suspension: 10 mg/mL
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	
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	
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	Adequate	Adequate per revision below: Each 1 mL of oral suspension contains 10 mg Sildenafil (equivalent to 14 mg Sildenafil citrate).

¹ Established name = [Drug] [Route of Administration] [Dosage Form]

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
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)	N/A	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	Shake well for at least 10 seconds before use.
For parenteral products: include statement: <i>"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"</i>	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	

For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement <i>“DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.x”</i> with x numerical citation to <i>“OSHA Hazardous Drugs”</i> .	N/A	

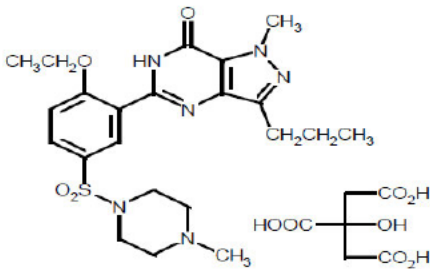
1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Oral suspension
Strength(s) in metric system	Adequate	10 mg/mL
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	Adequate	Adequate per revision below: Each 1 mL of oral suspension contains 10 mg Sildenafil (equivalent to 14 mg Sildenafil citrate).
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	white to off-white opaque suspension with a strawberry flavor
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

Section 11 (DESCRIPTION)

APPEARS THIS WAY ON ORIGINAL

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	LIQREV Sildenafil citrate
Dosage form(s) and route(s) of administration	Adequate	Oral suspension
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP . For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	Adequate	Each 1 mL of oral suspension contains 10 mg Sildenafil (equivalent to 14 mg Sildenafil citrate).
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	Adequate per revision below: The inactive ingredients include acesulfame potassium, citric acid monohydrate, glycerin, simethicone emulsion, sodium benzoate, sucralose, strawberry flavor, tri-sodium citrate dihydrate, xanthan gum, and water.
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	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Adequate	phosphodiesterase-5 (PDE-5) inhibitor

Chemical name, structural formula, molecular weight	Adequate	1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo [4,3-d] pyrimidin-5-yl)-4-ethoxyphenyl] sulfonyl]-4-methylpiperazine citrate and has the following structural formula:  It has a chemical formula of C₂₂H₃₀N₆O₄S. C₆H₈O₇ and a molecular weight of 666.7 g.mol⁻¹.
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Adequate	solubility of 3.5 mg/mL in water.

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling	N/A	



QUALITY ASSESSMENT



requirement may be applicable to another section of the PI (e.g., Section 2).		
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1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	Oral suspension
Strength(s) in metric system	Adequate	10 mg/mL
Available units (e.g., bottles of 100 tablets)	Adequate	amber glass bottle
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	white to off-white, opaque, strawberry-flavored suspension NDC 46287-055-01
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
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	
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.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures. ^x " with x numerical citation to "OSHA Hazardous Drugs."	Adequate	Shake well before use for at least 10 seconds. Use the bottle within 90 days once it has been opened.

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	Store from 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). [See USP for controlled room temperature].
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: <i>"Not made with natural rubber latex. Avoid statements such as "latex-free."</i>	N/A	
Include information about child-resistant packaging	Adequate	with a child resistant tamper-evident cap

1.2.5 Other Sections of Labeling**1.2.6 Manufacturing Information After Section 17 (for drug products)**

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	Distributed by: CMP Pharma, Inc. (b) (4) Farmville, NC 27828

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name ²	Adequate	LIQREV® (LIK-rev) (sildenafil) oral suspension
Special preparation instructions (if applicable)	Adequate	Shake LIQREV well (b) (4) (b) (4) before (b) (4)
Storage and handling information (if applicable)	Adequate	Store (b) (4) (b) (4) 68°F to 77°F (20°C to 25°C). (b) (4) (b) (4)
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	
Active ingredient(s) (if applicable)	Adequate	sildenafil citrate
Alphabetical listing of inactive ingredients (if applicable)	Adequate	Adequate per revision below: (b) (4)
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	CMP Pharma, Inc. (b) (4) Farmville, NC 27828

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CONTAINER AND CARTON LABELING

² Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name ³ , (font size and prominence)	Adequate	(b) (4)
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP .	Adequate	
Net contents (e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	
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, and these products require a "Not for direct infusion" statement.	N/A	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	

Linear Bar code	N/A	
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Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	Distributed by: CMP Pharma, Inc. Farmville, NC 27828
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	Adequate per revision below: (b) (4)
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
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.	N/A	
And others, if space is available.	N/A	Adequate per revision below: Specify the time of shaking Original: SHAKE WELL BEFORE USE. Revised: (b) (4)

³ Established name = [Drug] [Route of Administration] [Dosage Form]

Assessment of Carton and Container Labeling: *Adequate****Overall Assessment and Recommendation:***

**Adequate contingent upon accepting recommendations of this review.
Note that, at the time of filing this review, the labeling review is in progress**

Primary Labeling Assessor Name and Date:

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



Ali
Mohamadi

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Theodore
Carver

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NDA 214952: LIQREV (Sildenafil) Oral Suspension

OPQ Integrated Quality Review

Recommendation: Complete Response

Drug Name/Dosage Form	LIQREV (Sildenafil) Oral Suspension
Strength	10 mg of sildenafil (equivalent to 14 mg sildenafil citrate) per mL
Route of Administration	Oral
Indication	Indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) in adults to improve exercise ability and delay clinical worsening.
Rx/OTC Dispensed	Rx
Applicant	CMP Development LLC
Submissions (s) Reviewed	214952 resubmission and all subsequent CMC amendments

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Zhengfu Wang	CDER/OPQ/ONDP/DNDAPI/NDB3
Drug Product, Labeling	Ali Mohamadi	OPQ/ONDP/DNDPIII/NDPB5
Process and Facility	Carl Lee	OPQ/OPMA/DPMAIV/PMB12
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

Although the Office of Pharmaceutical Quality review team has assessed NDA 214952 with respect to drug substance, drug product, biopharmaceutics, and microbiology, and has determined that it meets all applicable quality standards for those disciplines, the (b) (4) (FEI (b) (4) drug substance manufacturing facility currently has unresolved deficiencies identified in a previous inspection and remains in OAI status. Satisfactory resolution of these manufacturing deficiencies and a satisfactory facility inspection are required before this application may be approved. Therefore, from the chemistry, manufacturing and controls (CMC)/quality perspective, this NDA is not recommended for approval in its present form.

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 LIQREV (Sildenafil) Oral Suspension 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) REVATIO (sildenafil) tablet, previously approved under NDA 021845, and b) in-vivo bioavailability studies. Sildenafil is a phosphodiesterase-5 (PDE-5) inhibitor indicated for the treatment of pulmonary arterial hypertension in adults, to improve exercise ability and delay clinical worsening.

B. Drug Substance (Sildenafil Citrate) : Dr. Zhengfu Wang reviewed the drug substance information and found it to be adequate. The drug substance DMF (b) (4) was found adequate in the previous review conducted by Dr. Wang, and the DMF remains adequate after review of subsequent amendments. The drug substance, sildenafil citrate USP, is a white to off-white hygroscopic crystalline powder, with a specification that conforms to the USP monograph and includes appropriate tests for critical quality attributes to ensure drug product quality, such as particle size distribution and polymorphism.

C. Drug Product (Sildenafil Oral Suspension): Dr. Ali Mohamadi reviewed the drug product information and found it to be adequate. The drug product information for this new sildenafil formulation was previously found adequate, and this review included new information for the drug

product specification and analytical procedures, xanthan gum excipient, extractable/leachables, and the risk assessment for potential (b) (4) impurities. The proposed drug product specification provides for appropriate control of sildenafil assay, impurities, (b) (4) content and microbiological quality, dissolution, deliverable volume, resuspendability, particle size based on (b) (4). The additional information regarding analytical procedures and extractables/leachables was reviewed and found to be adequate from a CMC perspective.

C.1 Manufacturing: Dr. Carl Lee reviewed the manufacturing process information and found it to be adequate. There are no changes to the manufacturing process in this resubmission. Additional information regarding executed batch records and process parameters was obtained through information requests and the proposed process and controls remain adequate.

C.2 Microbiological Aspects: The previous review found this NDA to be adequate with respect to microbiological quality and no new information was included in this resubmission. Therefore, see the previous microbiology review for more information.

C.3. Biopharmaceutics Aspects: The previous review found this NDA to be adequate with respect to biopharmaceutics, and no new information was included in the resubmission. Therefore, see the previous biopharmaceutics review for more information.

IV. Stability, Storage Conditions and Expiration Date

Stability data support the shelf-life of 24 months when the drug product is stored from 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). In-use stability studies confirmed that the drug product stays within specification for description, pH, assay, impurities, and microbiological tests up to 90 days after the bottle is opened.

V. Assessment of Manufacturing Facilities

The drug substance manufacturing and testing facility, (b) (4) (FEI: (b) (4)) was previously found to be non-compliant with GMP requirements. It remains noncompliant and currently has an (OAI) classification. The previous GMP deficiencies included inadequate investigation and controls to prevent presence of (b) (4) and (b) (4) in the drug substance, as well as poor maintenance of rusted equipment. (b) (4) did not resolve all of the GMP deficiencies and is still in OAI status. It will need to be reinspected to verify GMP compliance. The for-cause inspection will not be performed by the PDUFA goal date, and therefore, the recommendation for this facility is withhold approval.

In the previous integrated quality review of this NDA, deficiencies in the drug product manufacturing facility and a testing facility were noted. The deficiency in the drug product manufacturing facility was resolved through a preapproval inspection of the (b) (4) (FEI (b) (4)) completed during this review cycle, which resulted in an approval recommendation for this facility. In addition, a testing facility with deficiencies, (b) (4) (b) (4), was withdrawn, and the current facilities for conducting this testing are acceptable. See the table below for a summary of the status of manufacturing facilities for this NDA.

Table of Manufacturing Facilities for the NDA 214952 Resubmission:

Facility name and address	FEI	Responsibilities and profile code(s)	Status
(b) (4)			Approve - Based on PAI
			Withhold - Based on CGMP
			Withdrawn
			No Evaluation Necessary
			No Evaluation Necessary
CMP Pharma, Inc. 8026 US Highway 264A , Farmville, North Carolina, USA, 27828	1050589	Labeling Operations of Drug Product	Approve - Based on Previous History
(b) (4)			Approve - Based on Previous History

VI. Environmental Assessment

The applicant claims categorical exclusion from the environmental assessment requirements, under 21 CFR 314.50 (d) (1) (iii). This claim is found to be acceptable.

VII. Quality Labeling

No changes to the application were made in this resubmission, nor were any changes to the labeling required based on new information in this NDA resubmission. Therefore, see the previous integrated quality review for the review of the quality aspects of the labeling.

VIII. Life Cycle Knowledge Information See risk assessments included in the OPQ subdiscipline reviews.

IX. List of Deficiencies to be communicated to the ApplicantFacilities

1. During a recent inspection of the (b) (4) | FEI: (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. Please list communications submitted to, or held with, the Agency to facilitate resolution of the observed objectionable conditions, or deficiencies, noted at the facility.

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY**Application Technical Lead (ATL) Assessment and Signature:**

Based on the integrated quality review by the Office of Pharmaceutical Quality (OPQ), facility deficiencies currently remain unresolved for NDA 214952 for the drug substance manufacturing facility, (b) (4) (FEI (b) (4)), which has an official action indicated (OAI) classification. Satisfactory resolution of these deficiencies and a satisfactory inspection are required before this application may be approved. Therefore, OPQ recommends a Complete Response (CR) action from a product quality perspective.

Theodore Carver, Ph.D.

Senior Product Quality Assessor, OPQ/ONDP/DNDPIII/NDPB5



Theodore
Carver

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CHAPTER VI: BIOPHARMACEUTICS

[IQA NDA Assessment Guide Reference](#)

Product Information	Sildenafil Oral Suspension
NDA Number	NDA-214952-ORIG-1
Assessment Cycle Number	1
Drug Product Name/ Strength	Liqrev (Sildenafil Oral Suspension) 10 mg/mL
Route of Administration	Oral
Applicant Name	CMP Development LLC
Therapeutic Classification/ OND Division	Indicated for the treatment of pulmonary arterial hypertension (PAH)/ CDER/OND/OCHEN/DCN
RLD/RS Number	NDA 021845 (Revatio-Sildenafil Oral Tablets 20 mg)
Proposed Indication	It is a phosphodiesterase-5 (PDE-5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) in adults to improve exercise ability and delay clinical worsening.

Assessment Recommendation: Adequate

Assessment Summary: The Applicant, CMP Development LLC, is seeking approval of Liqrev (Sildenafil Oral Suspension) 10 mg/mL for the treatment of PAH. The new drug application, submitted in accordance with 505 (b)(2), references and relies on the safety and efficacy of REVATIO (sildenafil) 20 mg tablets [NDA 021845, approved on 06/03/2005] as the Listed Drug (LD). The Applicant conducted an in vivo bioequivalence study comparing the listed drug and the proposed drug, which is noted to be bioequivalent (BE) to the LD. The registration batches and proposed product for commercial manufacturing are same as the product or biobatch (VAL/18/0083) used in pivotal BE study. No manufacturing changes are noted.

The drug substance (API) demonstrates pH-dependent solubility, with high solubility in acidic conditions and low solubility in basic conditions (pH 6.8 buffer). Originally, the Applicant's proposed dissolution method was consistent with the FDA Dissolution database for Sildenafil Suspension for quality control of the proposed suspension product. In response to the Agency's IR, the Applicant has proposed a new dissolution method, as shown in Table 13, and demonstrated the discriminating ability of the method. The Applicant has provided full dissolution profile data for all exhibit batches. However, the Applicant's originally proposed acceptance criterion, "NLT ^{(b) (4)}% (Q) in ^{(b) (4)}min" was permissive, and therefore the Applicant was recommended to implement

tighter acceptance criterion, “NLT (b)(4)%(Q) in 20 min” in an IR. The Applicant has concurred with the recommended acceptance criterion of “NLT (b)(4)%(Q) in 20 minutes”. The Applicant’s proposed dissolution method and acceptance criteria are adequate. This Application, NDA 214952, is adequate and recommended for approval from a Biopharmaceutics perspective.

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
Particle Size Distribution	Medium	Particle size has the potential to impact drug release. It is noted that the dissolution method is able to discriminate between particle size. Additionally, a three-tier particle size distribution specification is set by the Applicant.	Low	The three-tier particle size distribution specification will be evaluated by the drug product reviewer.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
NDA-214952-ORIG-1 (Seq 0000)	10/5/20
NDA-214952-ORIG-1 (Seq 0006)	02/19/21
NDA-214952-ORIG-1 (Seq 0006)	03/19/21

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

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

B.1 BCS DESIGNATION

Assessment: Sildenafil citrate exhibits high solubility in the pH range of 1.2-5.0, but lower solubility at pH 6.8. Additionally, sildenafil citrate demonstrates

high permeability. Although the Applicant has claimed (b) (4) solubility, the data provided demonstrates that the drug substance belongs to BCS Class II.

Solubility: The drug substance (API) demonstrates pH-dependent solubility, with high solubility in acidic conditions and low solubility in basic conditions (pH 6.8 buffer). The Applicant has demonstrated that the drug substance achieves sink conditions in all conditions below pH 6.8, with maximum solubility demonstrated at pH 1.2. The Applicant has stated that Sildenafil belongs to (b) (4). Although the drug substance demonstrates high solubility in the (b) (4), it is noted that the drug substance is not soluble in less than 250 mL of media at the pH 6.8 range. Although the Applicant states that Sildenafil Citrate is (b) (4), the data below demonstrates that the drug substance belongs to BCS Class II.

Table 1: Solubility of Sildenafil Citrate

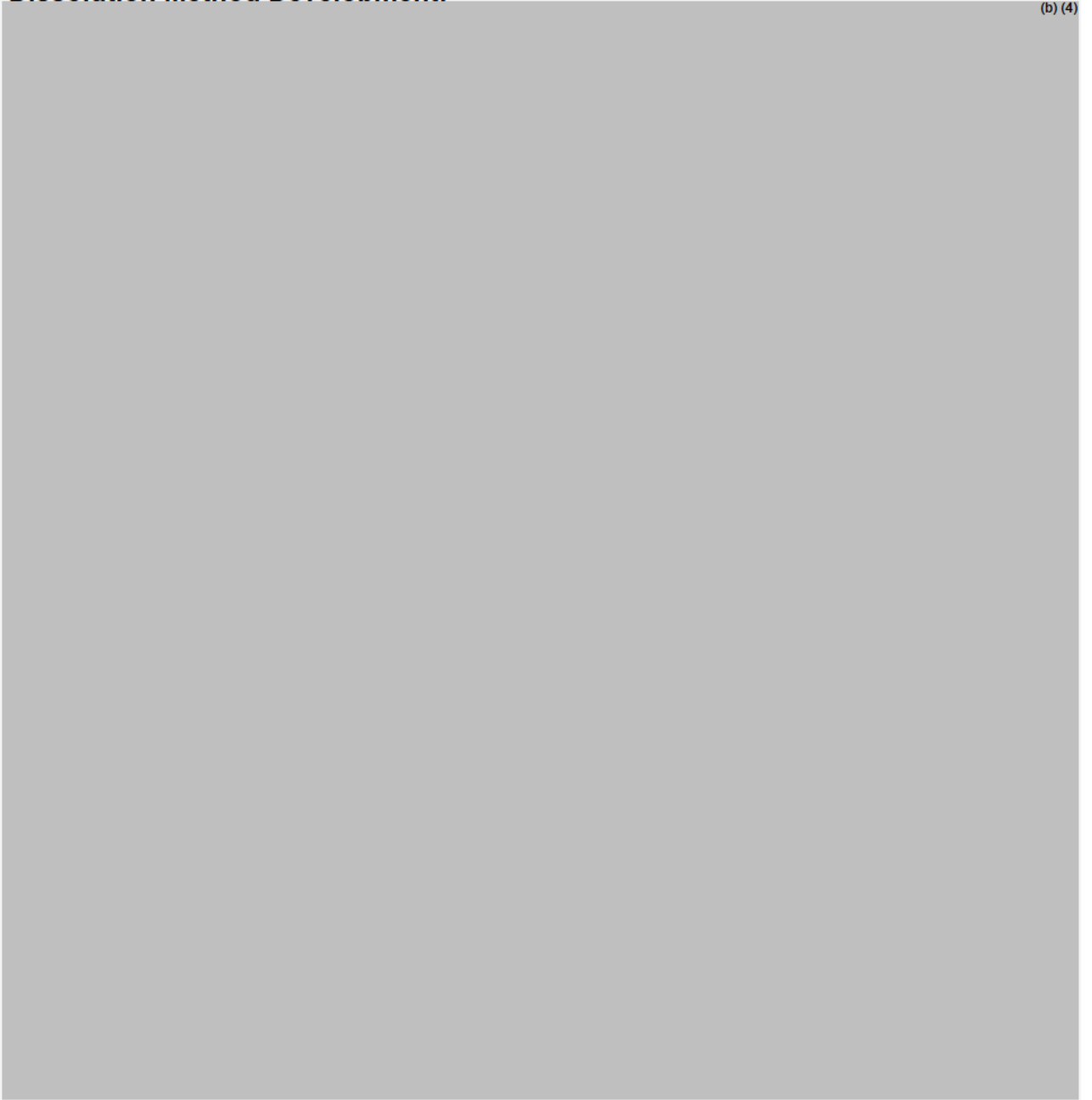
Name of media	Solubility (mg/mL)	Volume Required to Solubilize One Unit Dose (20 mg)	3x Volume to Solubilize Unit Dose	OGD recommended media volume	Sink condition
Buffer pH 1.2 - USP (Hydrochloric acid and Potassium chloride)	25	0.80 mL	2.40 mL	500 mL	Possible
Buffer pH 3.0 - McIlvaine's buffer (Citric acid and Phosphate)	0.5	40.0 mL	120.0 mL		Possible
Buffer pH 4.0 - McIlvaine's buffer (Citric acid and Phosphate)	0.7	28.6 mL	85.8 mL		Possible
Buffer pH 5.0 - McIlvaine's buffer (Citric acid and Phosphate)	1	20.0 mL	60.0 mL		Possible
Buffer pH 6.8 - USP (Phosphate and Sodium hydroxide)	0.05	400 mL	1200 mL		Not Possible
Purified water	3	6.67 mL	20.0 mL		Possible

Permeability: Not provided

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Dissolution Method Development:

(b) (4)



Discriminating ability of the Dissolution Method:

To investigate the discriminating ability of the originally proposed method, the Applicant has conducted comparative dissolution studies using aberrant formulations. The Applicant has chosen to vary the concentration of (b) (4) in the product because (b) (4) of the oral suspension and (b) (4)

Table 6a: Formulations for Comparative Dissolution Studies investigating the discriminating ability of the originally proposed dissolution method

API/Excipient	Formulation-1 (mg/mL) Proposed final formulation	Formulation-2 (mg/mL)
Batch No.	SILL1028	SILL1023
Sildenafil	10	10
Sodium benzoate	(b) (4)	
Xanthan gum		
Sucralose powder		
Acesulfame K		
Glycerin		
Citric acid monohydrate		
Tri sodium citrate dihydrate		
(b) (4) Simethicone		
Flavor		

Table 6b: Comparative Dissolution Studies investigating the discriminating ability of the originally proposed dissolution method to differentiate aberrant formulations

A) Sildenafil Oral Suspension 10 mg/mL (Batch No.: SILL1023) (Formulation-2 with (b) (4))						
Units	McIlvaine Buffer pH 5.0, 500 mL, Apparatus II (Paddles) at (b) (4) rpm					
	% Drug release at time points					
	05 min	10 min	15 min	20 min	30 min	45 min
1	(b) (4)					
2						
3						
4						
5						
6						
Mean	88.0	97.3	98.3	98.3	98.3	98.7
%RSD	2.2	1.1	1.2	1.0	0.9	0.6

Table 6c: Comparative Dissolution Studies investigating the discriminating ability of the originally proposed dissolution method to differentiate aberrant formulations

B) Sildenafil Oral Suspension 10 mg/mL (Batch No.: SILL1028) (Formulation-1 with (b) (4))						
Units	McIlvaine Buffer pH 5.0, 500 mL, Apparatus II (Paddles) at (b) (4) rpm					
	% Drug release at time points					
	05 min	10 min	15 min	20 min	30 min	45 min
1	(b) (4)					
2						
3						
4						
5						
6						
Mean	28.7	77.4	88.3	91.4	93.4	93.6
%RSD	20.8	3.4	1.8	1.8	1.3	1.2

Table 6d: Comparative Dissolution Studies investigating the discriminating ability of the originally proposed dissolution method to differentiate aberrant formulations

Test parameters	Specifications	Revatio for Oral Suspension Batch # B155303	Batch # SILL1026	Batch # SILL1027	Batch # SILL1028
	(b) (4)	Unknown	(b) (4) mg/mL	(b) (4) mg/mL	(b) (4) mg/mL
Description	White to off white suspension	White suspension	White suspension	White suspension	White suspension
Dissolution Media (McIlvaine buffer pH 5.0) ⁵	10 Min	86.9%	70.7%	18.0%	77.4%
	15 Min	95.2%	87.8%	31.7%	88.3%
	20 Min	98.0%	93.7%	77.3%	91.4%
	30 Min	101.1%	96.8%	88.4%	93.4%
	45 Min	101.4%	97.0%	93.8%	93.6%

It is noted that due to very rapid dissolution (> (b) (4) % in (b) (4) min) of the product, the originally proposed dissolution method was not able to discriminate against these aberrant formulations (b) (4) mg/mL, (b) (4) vs (b) (4). The Applicant has also conducted comparative dissolution studies to compare the proposed PSD of (b) (4) um with the high PSD of (b) (4) um.

Table 7a: Comparative Dissolution Studies investigating the discriminating ability of the originally proposed dissolution method to differentiate different PSD-Proposed oral suspension product ((b) (4) um)

McIlvaine Buffer pH 5.0, 500 mL, Apparatus II (Paddles) at (b) (4) rpm					
Units	% Drug release at time points				
	10 min	15 min	20 min	30 min	45 min (b) (4)
1					
2					
3					
4					
5					
6					
Mean	77.4	88.3	91.4	93.4	93.6
%RSD	3.4	1.8	1.8	1.3	1.2

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Table 7b: Comparative Dissolution Studies investigating the discriminating ability of the originally proposed dissolution method to differentiate different PSD-Formulation with higher PSD ((b) (4) um)

McIlvaine Buffer pH 5.0, 500 mL, Apparatus II (Paddles) at (b) (4) rpm					
Units	% Drug release at time points				
	10 min	15 min	20 min	30 min	45 min (b) (4)
1					
2					
3					
4					
5					
6					
Mean	29.5	42.9	73.8	89.7	96.0
%RSD	11.2	9.1	4.6	3.4	0.8

Table 7c: Comparative Dissolution Studies investigating the discriminating ability of the originally proposed dissolution method to differentiate different PSD

Test parameters	Specification	Revatio for Oral Suspension Batch # B155303	Sildenafil Oral Suspension Batch # SILL1012	Sildenafil Oral Suspension Batch # SILL1028
Description	White to off white suspension	White suspension	White suspension	White suspension
Assay of Sildenafil	(b) (4) %	(b) (4)		
Particle size distribution	d _{(b) (4)} :NMT (b) (4) μm	(b) (4)		
	d _{(b) (4)} :NMT (b) (4) μm			
	d _{(b) (4)} :NMT (b) (4) μm			
Dissolution (McIlvaine buffer pH 5.0)	(b) (4) Min			
	Min			
	20 Min			
	(b) (4) Min			
	Min			

Test Parameters	Specification	Batch # SILL1012	Batch # SILL1028
Particle Size Distribution	D (b) (4)	(b) (4) μm	(b) (4) μm

It is noted that due to rapid dissolution of the product the originally proposed dissolution method was not able to discriminate against these differences in particle size. In response to the Agency's IR, the Applicant conducted dissolution studies at (b) (4) and 35 RPM to determine if this rotational speed could be discriminating towards API particle size. To investigate the discriminating ability of the dissolution method with (b) (4) paddle speeds, the Applicant conducted comparative dissolution studies between two formulations with meaningful variations in particle sizes. See Table 8.

Table 8a: Formulations of Batches SILL1032 and SILL1044, 10 mg/mL Sildenafil Oral Suspension with varying particle sizes

Batch Number		SILL1032		SILL1044	
	Ingredient	Lot no	mg/mL	Lot no	mg/mL
1.	Sildenafil	1711123497	10.00	1611127120	10.00
2.	Sodium benzoate	0000995249	(b) (4)	0000995249	(b) (4)
3.	Xanthan gum (b) (4)	SB7091K		9L8952K	
4.	Sucralose (b) (4)	K43558094		K95653894	
5.	Acesulfame potassium	1702052		1912053	
6.	Glycerin	236735118JQ		275437103LR	
7.	Citric acid monohydrate	0000868931		0001023349	
8.	Tri-sodium citrate dihydrate	0000555088		0001045535	
9.	(b) (4) Simethicone emulsion	0008890670		H033153006	
10.	Strawberry flavor	10030262380		1004663481	
11.	Purified water	-	QS to 1 mL	-	QS to 1 mL
Particle Size Distribution of Sildenafil citrate (API)		1711123497	D (b) (4) μ m	16111127120	D (b) (4) μ m
			D μ m		D μ m
			D μ m		D μ m

Table 8b: Comparative Dissolution Studies of varying particle sizes at 35 RPM

Mellvaine buffer pH 5.0, 500 mL, Apparatus II (Paddle) at 35 rpm						
Batch no: SILL1032						
Assay of Sildenafil: (b) (4) %						
Units	Cumulative % Drug Released					
	5 min	10 min	15 min	20 min	30 min	45 min
Average	21.5	57.2	87.4	96.9	100.8	101.8
%RSD	10.1	11.8	2.3	1.8	1.4	2.3
Batch no: SILL1044						
Assay of Sildenafil: (b) (4) %						
Units	Cumulative % Drug Released					
	5 min	10 min	15 min	20 min	30 min	45 min
Average	13.7	23.8	35.7	48.8	84.1	98.5
%RSD	5.0	2.9	2.7	1.1	2.8	4.1

Table 8c: Comparative Dissolution Studies of varying particle sizes at

(b) (4)

Mellvaine buffer pH 5.0, 500 mL, Apparatus II (Paddle) at (b) (4)						
Batch no: SILL1032						
Assay of Sildenafil: (b) (4)						
Units	Cumulative % Drug Released					
	5 min	10 min	15 min	20 min	30 min	45 min
Average	13.1	23.3	37.8	58.3	79.0	86.8
%RSD	10.2	6.6	5.5	4.2	1.8	2.6
Batch no: SILL1044						
Assay of Sildenafil: (b) (4)						
Units	Cumulative % Drug Released					
	5 min	10 min	15 min	20 min	30 min	45 min
Average	10.3	21.4	29.9	39.8	61.8	89.2
%RSD	9.3	8.5	8.4	8.1	6.6	2.6

It is noted that both dissolution methods are able to discriminate API particle sizes since the dissolution profiles are not similar ($f_2 < 50$). To further study the discriminating ability of the dissolution method at (b) (4) paddle speed, the Applicant has conducted comparative dissolution studies of abberant formulations with varying (b) (4) concentrations. See Table 10. Additionally, the Applicant has set a three-tier PSD specification to be evaluated by the drug product reviewer (Table 9).

Table 9: Proposed Particle Size Distribution Specification

D (v, (b) (4))	Below (b) (4) μm
D (v, (b) (4))	Between (b) (4) μm to (b) (4) μm
D (v, (b) (4))	Between (b) (4) μm to (b) (4) μm

Table 10a: Abberant Formulations with Varying (b) (4) Concentrations

Batch Number		SILL1032		SILL1042	
Ingredient	Lot no	mg/mL	Lot no	mg/mL	(b) (4)
Particle Size Distribution of Sildenafil citrate (API)		1711123497	D (b) (4) μm D (b) (4) μm D (b) (4) μm	1811104939	D (b) (4) μm D (b) (4) μm D (b) (4) μm

Table 10b: Comparative Dissolution Studies of varying concentrations (Abberant Formulations) at

(b) (4)

Mellvaine buffer pH 5.0, 500 mL, Apparatus II (Paddle) at						
Batch no: SILL1032						
Assay of Sildenafil						
Units	Cumulative % Drug Released					
	5 min	10 min	15 min	20 min	30 min	45 min
Average	13.1	23.3	37.8	58.3	79.0	86.8
%RSD	10.2	6.6	5.5	4.2	1.8	2.6
Batch no: SILL1042						
Assay of Sildenafil						
Units	Cumulative % Drug Released					
	5 min	10 min	15 min	20 min	30 min	45 min
Average	8.9	15.2	21.2	27.8	42.3	66.5
%RSD	10.7	4.0	3.3	2.8	2.5	2.7

Table 10c: Comparative Dissolution Studies of varying concentrations (Abberant Formulations) at 35 RPM

(b) (4)

Mellvaine buffer pH 5.0, 500 mL, Apparatus II (Paddle) at 35 rpm						
Batch no: SILL1032						
Assay of Sildenafil						
Units	Cumulative % Drug Released					
	5 min	10 min	15 min	20 min	30 min	45 min
Average	21.5	57.2	87.4	96.9	100.8	101.8
%RSD	10.1	11.8	2.3	1.8	1.4	2.3
Batch no: SILL1042						
Assay of Sildenafil						
Units	Cumulative % Drug Released					
	5 min	10 min	15 min	20 min	30 min	45 min
Average	11.4	18.7	26.4	35.4	58.3	90.2
%RSD	6.9	4.1	3.1	2.7	1.9	2.0

Both (b) (4) tested (b) (4) 35 RPM) demonstrate discriminating ability towards abberant formulations of varying (b) (4) concentrations, as demonstrated with dissimilar dissolution profiles ($F2 < 50$). The Applicant has proposed using the 35 RPM dissolution method which meets their proposed specifications.

The proposed dissolution method demonstrates low variability and complete release ($> (b) (4) \%$) is seen by 15 minutes. The Applicant has demonstrated the discriminating ability of the method through comparative dissolution studies with aberrant formulations by changing the concentration of (b) (4) and API particle sizes.

Additional Comparative Dissolution Studies between Sildenafil Oral Suspension and Revatio (Sildenafil) Suspension Using the Proposed Dissolution Method:

In addition to the comparisons with the Listed Drug, the Applicant has conducted comparative dissolution studies with Revatio Oral Suspension and the proposed suspension product to help support the adequacy of the dissolution method. See Table 11.

Table 11: Comparative Dissolution between Sildenafil Oral Suspension and Revatio (Sildenafil) Suspension using the proposed dissolution method

Product	Cumulative % drug dissolved at (Time in minutes)							
	0	5	10	15	20	30	45	60
Sildenafil Oral Suspension 10 mg/mL, Batch # SILL1028								
Average %	0	28.7	77.4	88.3	91.4	93.4	93.6	94.3
RSD %	0	20.8	3.4	1.8	1.8	1.3	1.2	1.9
Revatio for Oral Suspension, Batch # B155303								
Average	0	55.8	86.9	95.2	98	101.1	101.4	102.2
RSD %	0	23.2	8.5	2.8	1.8	1.4	0.6	1.3

The Applicant has also conducted comparative dissolution studies between the proposed product and Revatio Oral Suspension in different drug release media of varying pH. See Table 12.

Table 12a: Comparative Dissolution between Sildenafil Oral Suspension and Revatio (Sildenafil) Suspension using (b) (4) N drug release medium

Product	Cumulative % drug dissolved at (Time in minutes)							
	0	5	10	15	20	30	45	60
Sildenafil Oral Suspension 10 mg/mL, Batch # SILL1028								
Average %	0	61.1	92.1	98.9	99.8	100.2	99.6	101.0
RSD %	0	14.2	1.6	1.8	1.4	1.8	1.2	0.6
Revatio for Oral Suspension, Batch # B155303								
Average %	0	27.8	49.3	82.8	93.8	102.9	102.2	101.8
RSD %	0	6.1	4.4	4.1	1.9	1.6	1.6	1.4

Table 12b: Comparative Dissolution between Sildenafil Oral Suspension and Revatio (Sildenafil) Suspension using (b) (4) drug release medium

Product	Cumulative % drug dissolved at (Time in Min)							
	0	5	10	15	20	30	45	60
Sildenafil Oral Suspension 10 mg/mL, Batch # SILL1028								
Average %	0	36.6	77.7	89.6	91.6	92.8	92.8	93.2
RSD %	0	46.8	7.0	1.6	1.7	2.6	1.9	2.2
Revatio for Oral Suspension, Batch # B155303								
Average %	0	13.5	24.2	38.7	56.0	88.0	98.6	99.4
RSD %	0	7.7	7.3	10.5	15.8	3.5	2.1	1.1

Table 12c: Comparative Dissolution between Sildenafil Oral Suspension and Revatio (Sildenafil) Suspension using pH (b) (4) drug release medium

Product	Cumulative % drug dissolved at (Time in Min)							
	0	5	10	15	20	30	45	60
Sildenafil Oral Suspension 10 mg/mL, Batch # SILL1028								
Average %	0	50.7	77.3	79.3	81.8	81.3	79.5	80.7
RSD %	0	32.5	7.6	6.8	3.7	3.2	4.4	3.3
Revatio for Oral Suspension, Batch # B155303								
Average %	0	17.4	30.1	49.3	68.4	74.8	78.0	77.9
RSD %	0	8.5	12.9	17.1	6.0	6.7	4.0	3.6

The drug release medium studies help support that Sildenafil Oral Suspension has rapid dissolution in all 4 dissolution mediums studied.

Dissolution Acceptance Criterion:

In response to the Agency's IR, the Applicant has provided full dissolution profile data for all three exhibit batches (VAL/18/0082, VAL/18/0083, VAL/18/0084) with the 35 rpm dissolution method. All Exhibit Batches demonstrate complete release ((b) (4) %) in 15 minutes. Therefore, the Applicant's proposed dissolution acceptance criterion, "NLT (b) (4) % (Q) in (b) (4) minutes" is permissive. The Applicant will be recommended to implement a dissolution acceptance criterion of "NLT (b) (4) % (Q) in 20 minutes". Additionally, this acceptance criterion is able to reject the aberrant batches with varying (b) (4) concentration and API particle size.

Assessment: {Adequate}

The Applicant has modified the originally proposed dissolution method in response to the Agency's IR asking for discriminating ability. The Applicant has demonstrated the discriminating ability of the proposed dissolution method towards aberrant formulations

of (b) (4). The Applicant has concurred with the recommended acceptance criterion of “NLT (b) (4) % (Q) in 20 minutes”. The Applicant’s proposed dissolution method and acceptance criteria are adequate.

Table 13: Approved Dissolution Method and Acceptance Criteria

Dissolution Conditions	Apparatus	USP-II (Paddle)
	Rotation Speed (RPM)	35 RPM
	Medium	Mcllvaine Buffer pH 5.0
	Volume	500 mL
	Temperature	37° ± °C
Acceptance Criteria	NLT (b) (4) % (Q) in 20 minutes.	

Table 14a: Exhibit Batch (VAL/18/0082) Dissolution Profile

Batch VAL/18/0082 (McIlvaine Buffer pH 5.0, USP-II (Paddle) RPM-35, Media volume: 500mL)																
	5	10	15	20	30	45	60									
1	(b) (4)							Manufacture Date: June 2018								
2								Dissolution Testing Date: 16 Feb 2021								
3								Batch Age at Testing: 02 Years 08 Months								
4																
5																
6																
7																
8																
9																
10																
11																
12																
Mean	32	65	88	94	97	97	98									
%RSD	21.2	18.8	3.7	1.6	0.8	0.5	0.9									
Max	(b) (4)															
Min																

Table 14b: Biobatch (VAL/18/0083) Dissolution Profile

Batch VAL/18/0083 (McIlvaine Buffer pH 5.0, USP-II (Paddle) RPM-35, Media volume: 500mL)														
	5	10	15	20	30	45	60							
1	(b) (4)							Manufacture Date: June 2018						
2								Dissolution Testing Date: 11 Feb 2021						
3								Batch Age at Testing: 02 years 08 months						
4														
5														
6														
7														
8														
9														
10														
11														
12														
Mean	26	68	90	97	100	100	101							
%RSD	10.2	19.0	4.6	1.9	0.8	0.7	0.8							
Max	(b) (4)													
Min														

Table 14c: Exhibit Batch (VAL/18/0084) Dissolution Profile

Batch VAL/18/0084, (McIlvaine Buffer pH 5.0, USP-II (Paddle) RPM-35, Media volume: 500mL)							
	5	10	15	20	30	45	60
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	30	63	90	99	103	101	100
%RSD	21.3	21.4	4.4	1.8	0.6	0.8	0.3
Max	(b) (4)						
Min							

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

Assessment: {Adequate/Inadequate}

In vivo BA/BE data are not available to demonstrate clinical relevance of the dissolution method and criteria.

B.12 BRIDGING OF FORMULATIONS

Assessment: {Adequate/Inadequate}

No bridging of formulations is necessary. The currently proposed drug product formulation is the same formulation used in the in vivo clinical studies. The proposed commercial manufacturing sites is the same as the used for clinical and registration batches.

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Poonam Delvadia, Ph.D.
06/04/2021



Poonam
Delvadia

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Date: 6/07/2021 09:50:16AM

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Nadia
Ahmed

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Date: 6/04/2021 04:38:49PM

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CHAPTER VII: MICROBIOLOGY

[IQA NDA Assessment Guide Reference](#)

Product Information	
NDA Number	214952
Assessment Cycle Number	1
Drug Product Name/ Strength	Sildenafil Oral Suspension, 10 mg/mL
Route of Administration	Oral
Applicant Name	CMP Development LLC
Therapeutic Classification/ OND Division	Phosphodiesterase (PDE) inhibitors/DCRP
Manufacturing Site	(b) (4)
Method of Sterilization	N/A. The subject drug product is non-sterile.

Assessment Recommendation: Adequate

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Seq 0000	10/05/2020
Seq 0009	03/12/2021

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

Remarks: The subject drug product is indicated for the treatment of pulmonary arterial hypertension in adults to improve exercise ability and delay clinical worsening. It is provided as a (b) (4) non-sterile, aqueous, oral suspension for multi-dose administration. A deficiency was conveyed to the applicant in an Information Request, dated 02 March 2021. The submission is **recommended** for approval on the basis of product quality microbiology.

Concise Description of Outstanding Issues: N/A.

Supporting Documents: N/A.

S DRUG SUBSTANCE- N/A. The subject drug product is non-sterile. Therefore, the drug substance manufacturing process and controls are not the subject of this product quality microbiology review.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –**

(See Seq 0000, Section 3.2.P.1, *Description and Composition of the Drug Product 0000* document)

The subject drug product is a white to off-white suspension.

- **Drug product composition –**

(See Seq 0000, Section 3.2.P.1, *Description and Composition of the Drug Product 0000* document)

Table 2 was provided for the finished drug product composition and reproduced below.

Table 2: Qualitative and Quantitative Composition and Function of Drug Product Ingredients

Ingredient	Quality Standard	Function	% w/v	Quantity/mL (mg/mL)
Sildenafil Citrate ¹	USP	API	1.00	10.00
Sodium Benzoate	NF	(b) (4)	(b) (4)	(b) (4)
Xanthan Gum (b) (4)	NF			
Sucralose	NF			
Acesulfame Potassium	NF			
Glycerin	USP			
Citric Acid Monohydrate	USP			
Tri-Sodium Citrate Dihydrate	USP			
(b) (4) Simethicone Emulsion	USP			
Strawberry Flavor	N/A	Flavoring Agent	Q.S. to 100.00%	Q.S. to 1 mL
Purified Water	USP	Vehicle		
Total			100.00%	1 mL

- **Description of container closure system –**

(See Seq 0000, Section 3.2.P.1, *Description and Composition of the Drug Product* document)

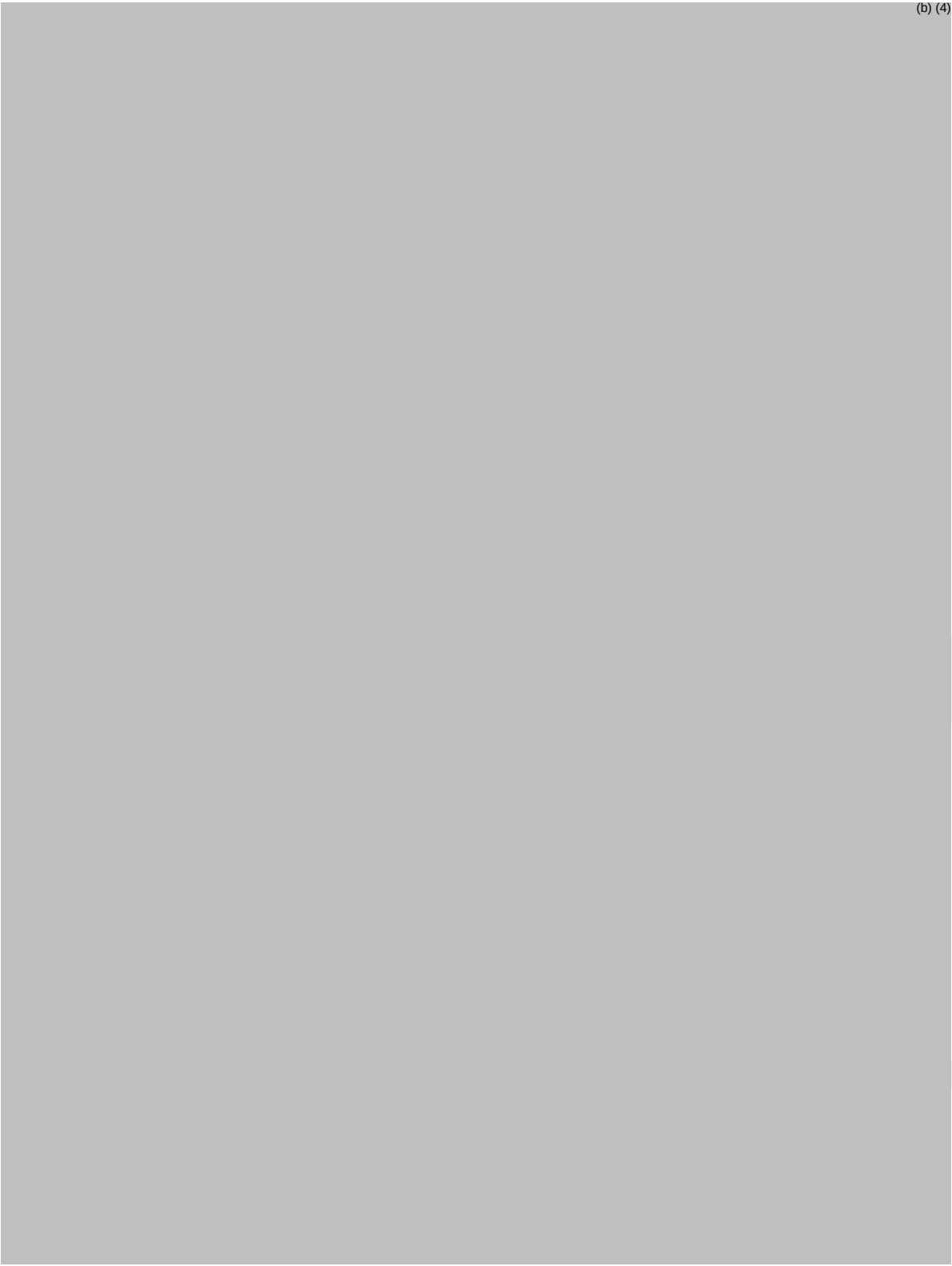
The drug product is packaged in a (b) (4) mL amber colored (b) (4) Glass Bottle with a (b) (4) white child resistant closure.

Assessment: Adequate

The applicant provided an adequate description of the drug product composition and the container closure system.

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)



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Christine
Craig

Digitally signed by Christine Craig
Date: 4/09/2021 08:38:20AM
GUID: 57ced2690109ab449e84a49141df01f8

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/

MOHAN K SAPRU
07/26/2021 07:07:43 AM

NDA 214952: LIQREV(Sildenafil) Oral Suspension

OPQ's Integrated Quality Review

Recommendation: Complete Response

Drug Name/Dosage Form	LIQREV (Sildenafil) Oral Suspension
Strength	10 mg of sildenafil (equivalent to 14 mg sildenafil citrate) per mL
Route of Administration	Oral
Indication	Indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) in adults to improve exercise ability and delay clinical worsening
Rx/OTC Dispensed	Rx
Applicant	CMP Development LLC
Submissions (s) Reviewed	214952 and all submitted CMC amendments

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Zhengfu Wang	OPQ/ONDP/DNDAP1/NDB3
Drug Product, Labeling	Ali Mohamadi	OPQ/ONDP/DNDP111/NDPB5
Process and Facility	Carl Lee	OPQ/OPMA/DPMA1V/PMB12
Biopharmaceutics	Nadia Ahmed	ONDP/DB/BB2
Microbiology	Daniel Schu	OPQ/OPMA/DMA1/MAB1
Application Technical Lead (ATL)	Mohan Sapru	OPQ/ONDP/DNDP111/NDPB5

Regulatory Business Process Manager: Grafton Adams; OPQ/OPRO/DRBPM1/RBPMB2

Related/Supporting Documents:

Document	Application Number	Description
DMF	Type II DMF# (b) (4)	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) existing official action indicated (OAI) classification for the drug substance manufacturing and testing facility, (b) (4) (FEI: (b) (4)) and product testing facility, (b) (4) (FEI: (b) (4)), and b) a 704(a)(4) review of (b) (4) (FEI: (b) (4)) has identified currently unresolved CGMP deficiencies, resulting in 'withhold' recommendation for the facility. Satisfactory resolution of these deficiencies is required before this application may be approved. Therefore, OPQ recommends 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 LIQREV(Sildenafil) Oral Suspension 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) REVATIO (sildenafil) tablet, previously approved under NDA 021845, and b) *in-vivo* bioavailability studies. Sildenafil is a phosphodiesterase-5 (PDE-5) inhibitor and relaxes the arterial wall, leading to decreased pulmonary arterial resistance and pressure.

1. Drug Substance (Sildenafil Citrate)

Sildenafil citrate, a white to off-white hygroscopic crystalline powder, is a compendial drug substance. The release specifications of the drug substance comply with current USP monograph. Particle size distribution is routinely tested on release. The CMC details about the drug substance such as structural characterization, manufacture and control strategies are cross-referenced to DMF (b) (4) which has been reviewed and found adequate. The drug substance exhibits polymorphism, which is controlled and tested by the drug substance manufacturer. 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 drug substance is packed into (b) (4)

(b) (4) The container closure is suitable for intended use and provides adequate

protection over the proposed retest period. The retest period of (b) (4) is supported by stability data.

2. Drug Product (Sildenafil Oral Suspension)

2.1. Product Design, and Release Specification: The drug product is a new formulation of sildenafil. 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. Except strawberry flavor, all excipients are compendial (USP-NF) and their levels are within limits of approved drugs. All ingredients contained in strawberry flavor are approved for use by the Agency or are considered as being generally recognized as safe (GRAS). Three excipients, sodium benzoate, citric acid monohydrate, and tri-sodium citrate dihydrate contain (b) (4). (b) (4) The calculated maximum amount of (b) (4) mg/day stays within the FDA's limit for (b) (4) /day, per CFR 73.1200(c). Each mL of sildenafil oral suspension contains 10 mg of sildenafil (equivalent to 14 mg sildenafil citrate). The suspension is packaged in (b) (4) mL Amber Colored (b) (4) glass bottles with a (b) (4) white child-resistant closures. Each bottle of the proposed drug product contains 122 mL of sildenafil suspension i.e., 1.22 g sildenafil (equivalent to 1.71 g sildenafil citrate) per bottle. The results from leachables and extractables studies and associated justifications are acceptable. The proposed container closure system is appropriate for the intended use.

The product release specification, involving testing of all the product critical quality attributes (CQAs), is adequate to ensure the consistent product quality. The unspecified and specified are controlled per ICH Q3B; calculated based on the maximum daily dose of 60 mg/day. No organic solvents are used to manufacture the drug product. The Applicant has provided risk assessment analyses for residual solvents and results show that the drug product complies with ICH Q3C. Therefore, a residual solvents test is not included in the drug product specification. Sodium benzoate levels are controlled at (b) (4) (b) (4)%, which is adequate for providing (b) (4). The non-compendial analytical procedures used for testing the drug product have been validated according to ICH guidelines. A risk assessment, per ICH guideline Q3D, regarding levels of elemental impurities in the drug product has been provided. 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.

2.2. Manufacturing: Briefly, the product manufacturing includes (b) (4). (b) (4) Adequate information has been provided about incoming materials and unit operations. The critical process parameters and in-process control limits for different unit operation are adequate. The level of viscosity is controlled with the viscosity limit of (b) (4) cps at the (b) (4). Process scale-up is < (b) (4)X for the (b) (4)L batch size. Equipment used for submission batch

manufacturing will be used for commercial manufacturing, and the process parameters and controls are similar. Overall, the manufacturing process is well-controlled.

2.3. Microbiological Aspects: The proposed formulation is intended to be provided as a (b) (4) non-sterile, aqueous, oral suspension for multi-dose administration. Microbiological testing is done on release per USP <61>, <62> and <1111>. Sodium benzoate is included as a (b) (4) in the formulation. Results from antimicrobial effectiveness testing (AET), performed per USP <51>, are adequate. The Applicant's proposed microbiological tests, test methods, and acceptance criteria are consistent with regulatory expectations for a (b) (4) non-sterile, aqueous drug product for oral administration.

2.4. Biopharmaceutics Aspects: Although the Applicant has claimed (b) (4) solubility for sildenafil citrate, the data provided demonstrate that the drug substance belongs to BCS Class II. The Applicant has conducted comparative dissolution studies between the proposed product and the Listed Drug. Per revised dissolution method, the Applicant has demonstrated the discriminating ability of the dissolution method and proposed acceptance criteria are adequate. No bridging of formulations is necessary because the currently proposed drug product formulation is the same formulation used in the *in vivo* clinical studies. Additionally, the proposed commercial manufacturing sites is the same as the used for clinical and registration batches.

2.5. 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 are permitted to 15°C to 30°C (59°F to 86°F).

2.6. Assessment of Manufacturing Facilities

- Drug substance manufacturing and testing facility, (b) (4) (FEI: (b) (4)), which is currently non-compliant with GMP requirements, has under the official action initiated (OAI) classification. The GMP deficiencies include inadequate investigation and controls to prevent presence of (b) (4) in API as well as poor maintenance of rusted equipment.
- Product testing facility, (b) (4) Limited (FEI: (b) (4)), which is currently non-compliant with GMP requirements, has the official action initiated (OAI) classification.
- Drug product manufacturing and testing facility, (b) (4) (FEI: (b) (4)), is deemed high risk because the facility has never been inspected before by FDA. A 704(a)(4) review of the facility has identified significant 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, which include lack of microbial controls and cross-

contamination concerns, have been reviewed but critical outstanding concerns remain unresolved. Thus, the identified deficiencies are currently unresolved, resulting in 'withhold' recommendation for (b) (4) (FEI: (b) (4)).

3. Environmental Assessment

The applicant's claim of categorical exclusion from the environmental assessment requirements, under 21 CFR 314.50 (d) (1) (iii), is acceptable.

4. List of Outstanding Facility Deficiencies to be Communicated to the Applicant:

Facility Inspections:

- i. During a review of records requested under section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act, the FDA noted objectionable conditions and communicated deficiencies to (b) (4) FEI (b) (4) manufacturing facility that is listed in your application. Satisfactory resolution of currently unresolved issues is required 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) (b) (4) FEI (b) (4) manufacturing facility for additional information. An inspection of the (b) (4) FEI (b) (4) facility is required before the application can be approved. FDA must ensure that the facility is able to conduct the listed manufacturing operations in compliance with CGMP. Due to restrictions on travel, we may be unable to conduct an inspection of the (b) (4) (b) (4) facility prior to 8/5/2021. 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/emergency-preparedness-andresponse/coronavirus-disease-2019-covid-19/covid-19-relatedguidancedocuments-industry-fda-staff-and-other-stakeholders>.
- ii. During a recent inspection of the (b) (4) FEI: (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. Please list communications submitted to or held with the Agency to facilitate resolution of the observed objectionable conditions, or deficiencies, noted at the facility.
- iii. During a recent inspection of the (b) (4) FEI: (b) (4) testing 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. Please list

communications submitted to or held with the Agency to facilitate resolution of the observed objectionable conditions, or deficiencies, noted at the facility.

5. Life Cycle Knowledge Information

Final Risk Assessment

NDA 214952: LIQREV(Sildenafil) Oral Suspension

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
Drug Substance and Drug Product Manufacturi ng	• Manufacturing Facilities • Manufacturing Process • Control Strategies	High	(b) (4)	Not acceptable	
Physical Stability (phase separation)	• Formulation • Raw materials • Process parameters • Scale/ equipment/ site	Low (L)		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/equipme nt/site	Low (L)		Acceptable	N/A

Attribute/ CQA	Factors Impacting CQAs	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations
Palatability	• Formulation • Excipient change • Process parameters Scale/equipment/site	Moderate (M)	(b) (4)	Acceptable	N/A
Leachables	• Formulation • Container closure • Process parameters Scale/equipment/site	Moderate (M)		Acceptable	N/A
Microbial limits	• Formulation • Raw materials • Process parameters Scale/equipment/site	Low (L)		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) existing official action indicated (OAI) classification for the drug substance manufacturing and testing facility, (b) (4) (FEI: (b) (4)) and product testing facility, (b) (4) (FEI: (b) (4)), and b) a 704(a)(4) review of (b) (4) (FEI: (b) (4)) has identified currently unresolved CGMP deficiencies, resulting in 'withhold' recommendation for the facility. Satisfactory resolution of these deficiencies is required before this application may be approved. Therefore, OPQ recommends Complete Response (CR) action from a product quality perspective.

Mohan Sapru, M.S., Ph.D.
Branch Chief, Branch 5
Division of New Drug Products III
CDER/OPQ/ONDP/DNDPIII/NDPB5

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Patient labeling

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	LIQREV	Adequate
Established name(s)	(sildenafil) oral suspension.	Adequate per revision
Route(s) of administration	oral suspension	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Oral (b) (4) (b) (4) 20 mg three times a day, (b) (4) (b) (4)	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Adequate
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	Adequate

1.2 FULL PRESCRIBING INFORMATION

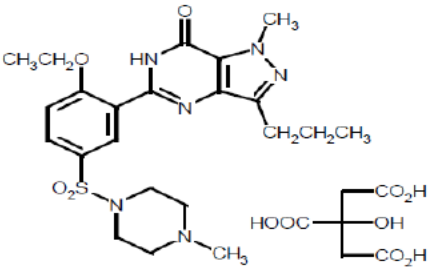
1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation	The recommended dose of LIOREV is (b) (4) 20 mg orally (b) (4) three times a day. (b) (4) Shake well for at least 10 seconds before use.	Adequate per revision

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Oral Suspension	Adequate
Strength(s) in metric system	10 mg (b) (4) mL	Adequate per revision
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	The name and strength are expressed based on the neutral form, sildenafil, consistent with the listed drug.	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	white to off-white opaque suspension with a strawberry flavor.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Adequate
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	Adequate

Item	Information Provided in the NDA	Comments
DESCRIPTION section		
Proprietary and established name(s)	LIQREV (sildenafil) Oral Suspension	Adequate
Dosage form(s) and route(s) of administration	(b) (4) oral	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Equivalency statement is added: Each bottle contains 1.22 g Sildenafil (equivalent to 1.71 g Sildenafil citrate).	Adequate per revision
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	The inactive ingredients include sodium benzoate, xanthan gum, sucralose, acesulfame potassium, glycerin, citric acid monohydrate, tri-sodium citrate dihydrate, simethicone (b) (4) emulsion, strawberry flavor, and water.	Adequate per revision
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	Adequate
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	Adequate
Statement of being sterile	N/A	Adequate
Pharmacological/therapeutic class	a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type-5 (PDE-5).	Adequate

Chemical name, structural formula, molecular weight	Sildenafil citrate is a white to off-white crystalline powder with a solubility of 3.5 mg/mL in water. It has a chemical formula of $C_{22}H_{30}N_6O_4S \cdot C_6H_8O_7$ and a molecular weight of 666.7 gr.mol⁻¹. 	Adequate per revision
If radioactive, statement of important nuclear characteristics.	N/A	Adequate
Other important chemical or physical properties (such as pKa or pH)	Sildenafil citrate is a white to off-white crystalline powder with a solubility of 3.5 mg/mL in water	Adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	Adequate
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	Adequate

1.2.3 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Oral Suspension	Adequate
Strength(s) in metric system	10 mg/mL	Adequate
Available units (e.g., bottles of 100 tablets)	It is available in a ~~422 mL~~ amber glass bottle with a child resistant tamper-evident cap (NDC 46287-055-01).	Adequate per revision
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	N/A	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Adequate
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	Adequate

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
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.)	Shake well before use for at least 10 seconds. (b) (4) (b) (4)	Adequate per revision
If the product contains a desiccant, ensure the size and shape differ from the	N/A	Adequate

dosage form and desiccant has a warning such as "Do not eat."		
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store from 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). [See USP for controlled room temperature]. Use the bottle within 90 days once it has been opened. (b) (4)	Adequate per revision
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."	N/A	Adequate
Include information about child-resistant packaging	It is available in a ~~122 mL~~ amber glass bottle with a child-resistant tamper-evident cap (NDC 46287-055-01).	Adequate per revision

1.2.4 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
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	Adequate

2.0 PATIENT LABELING

Use the bottle within 90 days once it has been opened. Was added

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): N/A

CARTON AND CONTAINER LABELING



Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	(b) (4)	Adequate per revision: Liqrev (Sildenafil) Oral Suspension
Dosage strength		Adequate
Route of administration		Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance		Adequate per revision: Each mL (b) (4) (b) (4) contains 10 mg of sildenafil (b) (4)
Net contents (e.g. tablet count)	N/A	Adequate
"Rx only" displayed on the principal display	Included	Adequate
NDC number	Included	Adequate
Lot number and expiration date	Included	Adequate

Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 20° C –25° C (68° F–77° F); excursions permitted to 15° C–30° C (59° F–86° F). [See USP Controlled Room Temperature].	Adequate per revision: Change to: Store (b) (4) 20 °C to 25 °C (68 °F to 77 °F); excursions permitted to 15 °C to 30 °C (59 °F to 86 °F) . [see USP Controlled Room Temperature]
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	Adequate
Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	N/A	Adequate

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	Adequate
Bar code	Included	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	(b) (4)	Adequate
Medication Guide (if applicable)		Adequate
No text on Ferrule and Cap over seal	N/A	Adequate
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.	N/A	Adequate
And others, if space is available	None	Adequate

Assessment of Carton and Container Labeling: Adequate

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor Name and Date:

Ali Mohamadi, Ph.D., 5/25/2021

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



Ali
Mohamadi

Digitally signed by Ali Mohamadi
Date: 6/08/2021 02:54:40PM
GUID: 508da6ea0002750ec7c6cb7cfc37f10e



Mohan
Sapru

Digitally signed by Mohan Sapru
Date: 6/16/2021 12:56:35PM
GUID: 504f821600000ec6d20b59d2b68eb3d2