# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 214522Orig1s000

# PRODUCT QUALITY REVIEW(S)

# NDA 214522 Resubmission

# TADLIQ™ (tadalafil) Oral Suspension

# Integrated Quality Review

## Quality Recommendation: Approval

| | |
|---|---|
| Drug Name | TADLIQ™ (tadalafil) oral suspension |
| Indication | Treatment of pulmonary hypertension to improve exercise ability |
| Dosage form | Oral Suspension |
| Strength | 20 mg/5 mL |
| Route of Administration | Oral |
| Rx/OTC Dispensed | Rx |
| Applicant | CMP Develoment, LLC. |
| US agent, if applicable | N/A |
| Submission (s) Reviewed | NDA 214522 resubmission (Supporting Document 15) and all subsequent CMC amendments |

## Quality Review Team

| DISCIPLINE | REVIEWER | BRANCH/DIVISION |
|---|---|---|
| Drug Substance | Sithamalli Chandramouli | OPQ/ONDP/NDAB3 |
| Drug Product, Labeling, and Environmental Assessment | Theodore Carver | OPQ/ONDP/DNDPIII/NDPB5 |
| Process and Facility | Upasana Sahu | OPQ/OPMA/DPMAIV/PMB12 |

| | | |
|---|---|---|
| Biopharmaceutics | Parnali Chatterjee | OPQ/ONDP/DB/BB3 |
| Microbiology | Jianli Xue | OPQ/OPMA/DMAI/MAB2 |
| Regulatory Business Process Manager | Grafton Adams | OPQ/OPRO/DRBPMI/RBPMB2 |
| Application Technical Lead | Theodore Carver | OPQ/ONDP/DNDPIII/NDPB5 |

# EXECUTIVE SUMMARY

## 1. Recommendation and Conclusion on Approvability

The Office of Pharmaceutical Quality Review team has assessed NDA 214522 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.

## 2. Background Summary

The Applicant, CMP Development, Ltd., is seeking U.S. marketing approval for Tadalafil Oral Suspension, 20 mg/5 mL, in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. Tadalafil Oral Suspension is indicated for pulmonary arterial hypertension. For the approval of this NDA, the Applicant relies on FDA's previous finding of safety and efficacy for the listed drug (LD), ADCIRCA® (Tadalafil) tablets, NDA 022332, held by Eli Lilly and Company. In addition, this application contains supporting in vivo bioavailability studies. The proposed product is a liquid oral formulation that is intended to be easier to administer for patients with difficulty swallowing tablets. In comparison with the listed drug, the route of administration and dose of Tadalafil Oral Suspension are the same as for the reference product, but the dosage form, formulation and composition are different. The previous Integrated Quality Review, dated 02/21/2021, concluded that the application was not approvable due to issues with a drug product manufacturing facility and a drug substance testing facility. The Applicant has resubmitted NDA 214522 with new facility information and other revisions to address the product quality issues identified in the last review.

## 3. Summary of Quality Assessment

Tadalafil oral suspension, a new dosage form and formulation of Tadalafil USP, is a white to off-white aqueous suspension to be marketed as a single strength of 20 mg/5mL (4 mg/mL). The drug product contains excipients that contribute to maintaining the quality of the drug product in suspension form during storage and use, including (b) (4) mg/mL glycerin, (b) (4) mg/mL xanthan gum, (b) (4) mg/ mL polysorbate 80, and (b) (4) mg/mL simethicone emulsion. In addition, the product is (b) (4) citric acid monohydrate and trisodium citrate

dihydrate, (b) (4) sodium benzoate (b) (4) peppermint flavor (b) (4) . The product is packaged in 150 mL (b) (4) bottles with a white plastic cap. No dosing device is co-packaged with the drug product. In the resubmission that is the subject of this review (Resubmission 15), the Applicant has addressed issues from the last review of the original NDA regarding the manufacturing and testing facilities and as other concerns related to drug product manufacturing; therefore, all product quality aspects of this NDA are adequate to support approval.

### 3.1. Drug Substance (Tadalafil)

Dr. Sithamalli Chandramouli reviewed the tadalafil drug substance and it remains adequate. The drug substance, tadalafil USP, Pyrazino [1', 2':1, 6] pyrido [3, 4-b] indole-1, 4-dione, 6-(1, 3-benzodioxol-5-yl)-2, 3, 6, 7, 12, 12a-hexahydro-2-methyl-(6R, 12aR), is referenced to DMF (b) (4) for chemistry, manufacturing, and controls information. This DMF including amendments has been reviewed and remains adequate to support this NDA. The drug substance conforms to the USP monograph for tadalafil, USP. Because a drug substance testing site (b) (4) was withdrawn, verification protocols and reports for the new test states performing testing of the drug substance (b) (4). and (b) (4) were reviewed and found to be adequate. See the previous Integrated Quality Review (02/12/21) for more information regarding the drug substance.

### 3.2. Drug Product (Tadalafil oral suspension)

**A) Product Design and Specifications:** The drug product is an aqueous suspension intended for oral administration at a single strength of 20 mg/5 mL (4 mg/mL). Dr. Theodore Carver performed the review of the drug product. The tadalafil oral suspension was developed as an alternative oral dosage form for patients with dysphagia (difficulty swallowing). The recommended daily dose for TADLIQ™ (tadalafil) Oral Suspension is 40 mg (10 mL) to be taken once daily with or without food. Since the tadalafil drug substance is practically insoluble in water, the drug product is manufactured as a liquid suspension of tadalafil with (b) (4) (b) (4). Critical quality attributes of the drug product include particle size, suspension uniformity, palatability, microbiological properties, and stability, which were evaluated as part of the (b) (4) . In terms of composition, the drug product contains 4 mg/mL tadalafil (USP) as the active ingredient, (b) (4) mg /mL sodium benzoate (NF) (b) (4), (b) (4) mg/mL xanthan gum (NF) as a (b) (4) (b) (4) mg/mL sucrose (NF) (b) (4) (b) (4) mg/mL glycerin (USP) as (b) (4), (b) (4) mg/ mL citric acid monohydrate (USP) as (b) (4), (b) (4) mg/mL trisodium citrate dihydrate (USP) (b) (4), (b) (4) mg/mL polysorbate 80 (NF) as a (b) (4), (b) (4) mg/mL 30% simethicone emulsion (USP) as (b) (4), and peppermint flavor (referenced to DMF as (b) (4); these ingredients are (b) (4) The container closure system consists of 150 mL (b) (4) bottles with white (b) (4) caps (b) (4) The drug product specification includes appropriate tests and acceptance criteria with respect to the identity, potency, and purity of the drug product based on its Quality Target Product Profile (QTPP), including viscosity, resuspendability, and suspension testing to

confirm that the oral suspension retains the physicochemical attributes required for correct dosing both at release and during storage. The drug product is resuspended by shaking the bottle before each use, and the shaking time specified in the labeling (30 seconds) is supported by release and stability data submitted to the NDA. In this NDA resubmission, the Applicant added a test for particle size of the drug product to the drug product specification, based on data from development and registration batches. The test method and acceptance criteria were reviewed and found to be adequate. Stability data support a shelf life of 24 months storage at 20ºC to 25 ºC.

**B) Drug Product Manufacturing**: Dr. Upasana Sahu performed the review of the drug product manufacturing process in this NDA resubmission. Tadalafil oral suspension is manufactured by (b) (4) (b) (4) (b) (4). The conclusion of the review of the manufacturing process information is that it is adequate because all deficiencies, including facility deficiencies identified in the first review, have been addressed.

**C) Biopharmaceutics Aspects:** Dr. Parnali Chatterjee performed the biopharmaceutics review. There were no changes in the supporting biopharmaceutics data or test method since the previous review, and therefore the drug product remains adequate with respect to biopharmaceutics. See also IQA dated 02/12/2021.

**D) Microbiological Aspects:** There were no changes in the (b) (4) and supporting data relating to microbiological aspects of the drug product, which were reviewed by Dr. Jianli Xue. See also IQA dated 02/12/2021.

**E) Container Closure System:** The drug product is light sensitive based on photostability studies and is packaged in a suitably light-resistant container closure system, amber bottles with opaque, child-resistant caps. The total volume of the bottle is 172 mL with a 150 mL fill volume.

## 4. Assessment of Manufacturing Facilities

The overall manufacturing inspection recommendation (OMIR) from the Office of Process Manufacturing Assessment (OPMA) for this NDA is Approval. Dr. Upasana Sahu reviewed the facility compliance information for the drug substance and drug product. In the previous review,

the drug product manufacturing facility, (b) (4) were found to be deficient with major deficiencies (see IQA dated 02/12/2021). The (b) (4) facility was not GMP-compliant and had OAI status. During review of the NDA resubmission, a preapproval inspection (PAI) was conducted at the (b) (4). facility, which was found to be acceptable with VAI indicated. In addition, the Applicant has withdrawn the (b) (4) facility from the NDA in this resubmission. The drug substance and drug product testing previously performed at the (b) (4) facility is now performed at (b) (4) and (b) (4) which are GMP-compliant with acceptable status. Therefore, the major facility deficiencies identified in the previous review have been addressed and all facilities are now acceptable. The overall recommendation for the manufacturing facilities for this NDA is Approval. See the table below and he attached OPMA review for summaries of the facilities supporting this NDA.

| Facility name and address | FEI | Responsibilities | Status |
|---|---|---|---|
| (b) (4) | | | Approve - Based on PAI |
| | | | Approve - Based on Previous History |
| | | | No Evaluation Necessary |
| CMP Pharma, Inc.<br><br>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 |

## 5. Expiration Date & Storage Conditions

The Applicant proposes a 24-month shelf life based on 12 months long-term and 6 months accelerated stability data, for 3 batches manufactured at the (b) (4) commercial scale. No trending or anomalous results were observed for any test on stability, for any storage condition. Based on available stability data, an expiration period of 24 months is granted when stored at 20°C to 25°C (68°F to 77°F) in commercial packaging, with excursions permitted to 15°C to 30°C (59°F to 86°F).

## 6. Environmental Assessment

The Applicant requested a Categorical Exclusion [21 CFR 314.50 (d) (l) (iii)] in that this drug product will not be administered at higher dosage levels, for longer duration, or for different indications than were previously in effect. The Applicant stated that, to the Applicant's knowledge, no extraordinary circumstances exist. This claim is acceptable for this 505(b)(2) application.

## 7. Quality Labeling

The container and carton label were reviewed as part of the previous drug product review (see IQA dated 02/12/2021). There were no changes in the drug product or labeling requiring review, therefor the labeling remains adequate.

## OVERALL ASSESSMENT AND FINAL RECOMMNDATION

**Application Technical Lead (ATL) Assessment and Signature:**

At present, there are no outstanding deficiencies related to the drug substance, drug product, biopharmaceutics, microbiology, manufacturing, and environmental assessment sections of this NDA. The OPQ overall recommendation for NDA 214522 is approval.

Theodore E. Carver -S

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Date: 2022.05.27 16:51:21 -04'00'

Theodore Carver, Ph.D.
Application Technical Lead (ATL)
Review Chemist
ONDP/DNDPI/NDPBV

# Life Cycle Knowledge Management

## Final Risk Assessment: NDA 214522

## TADLIQ™ (tadalafil) Oral Suspension

| Product Property/ *CQAs* | Factors that can Impact the CQAs | Initial Risk Ranking | Risk Mitigation Approach | Final Risk Evaluation | Comment |
|---|---|---|---|---|---|
| Assay, Stability | • Formulation<br>• Container closure<br>• Raw materials<br>• Process parameters<br>• Scale/equipment/ site | Medium | (b) (4) | **Acceptable** | Facilities for drug product manufacturing and testing are approved based on PAI. |
| Physical stability (suspension) | • Formulation<br>• Raw materials<br>• Process parameters<br>• Scale/equipment/ site | Medium | | **Acceptable** | Facilities for drug product manufacturing and testing are approved based on PAI |
| Dosing Accuracy | • Formulation<br>• Raw materials<br>• Process parameters for mixing | Low | | **Acceptable** | |
| pH | • Formulation<br>• Raw materials<br>• Process parameters<br>• in-process controls | Low | | **Acceptable** | |

| | | | | | |
|---|---|---|---|---|---|
| Microbiological quality | • Formulation<br>• Raw materials<br>• Preservative content | Low | (b) (4) | **Acceptable** | |
| Palatability | • Formulation<br>• Excipient selection<br>• Process parameters<br>• Scale/equipment/ site | Low | | **Acceptable** | |
| Dissolution | • Formulation<br>• Raw materials<br>• Process parameters<br>• Scale/equipment/ site | Low | | **Acceptable** | Facility for drug product testing are approved based on PAI |
| Leachables | • Formulation<br>• Container closure | | | **Acceptable** | Formulation is similar to an oral aqueous formulation. |

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# CHAPTER VII: BIOPHARMACEUTICS MEMO

**NDA:** 214522-ORIG-1-RESUB-15
**Drug Product Name / Strength:** TADLIQ™ (tadalafil) Oral Suspension, 4 mg/mL
**Route of Administration:** Oral
**Applicant Name:** CMP Development, LLC
**Primary Reviewer**: Parnali Chatterjee, Ph.D.
**Secondary Reviewer**: Haritha Mandula, Ph.D.

***Background:***
NDA 214522-ORIG-1 was originally submitted on 04/23/2020 to seek regulatory approval of TADLIQ™ (tadalafil) Oral Suspension, 4 mg/mL for the treatment of pulmonary arterial hypertension (PAH) to improve exercise ability *via* the 505 (b)(2) regulatory pathway. However, deficiencies were identified with the manufacturing facility and Chemistry, Manufacturing, and Controls (CMC) of the proposed drug product in the Complete Response Letter (CRL) dated 02/23/2021.

To address the deficiencies in the CRL, the Applicant resubmitted the NDA 214522-ORIG-Resub-15 on 12/21/2021.

***REVIEW SUMMARY:***
The proposed to-be-marketed (TBM) drug product is a white to off-white suspension containing tadalafil [a white, crystalline (b) (4) non-hygroscopic, racemic drug substance], sodium benzoate, xanthum gum, sucralose, polysorbate 80, and other excipients filled in 150 mL (b) (4) The pH of the drug product is maintained between (b) (4).

The NDA relied up on the FDA's findings of safety and efficacy conducted with the LD, ADCIRCA™, 20 mg [NDA 022332 approved on 05/22/2009]. In the original submission, the NDA was also supported by a comparative open-label, randomized, single-dose, two treatment, three sequence, three period, crossover bioequivalence (BE) study 19-016 conducted with 5 mL (equivalent to 20 mg tadalafil) of the proposed drug product batch VAL/18/0103 and 20 mg Listed Drug (LD), ADCIRCA™ in healthy, adult, human subjects under fasting and fed conditions to provide a pharmacokinetic bridge.

- ***Acceptable Dissolution Method and Dissolution Acceptance Criterion:***

Dissolution testing was identified as a critical quality attribute (CQA) and utilized as a quality control tool throughout the product development process, manufacturing process development and optimization, for release of batches used in the pivotal clinical PK study, for batches on long-term and accelerated stability conditions, and will be used for life-cycle management of the proposed drug product.

Tadalafil is a crystalline (b) (4) racemic drug substance that demonstrates pH-independent, rate-limiting, low aqueous solubility (0.01 mg/mL) in buffer solutions across the physiological pH range 1.2-6.8.

(b) (4)

Taking into consideration the overall dissolution data provided for the bio-batch and registration batches of the proposed drug product, the following dissolution method and acceptance criterion were deemed acceptable for dissolution testing of 5 mL (20 mg) of the proposed drug product in the original submission:

| **ACCEPTABLE** Dissolution Method and Acceptance Criterion | |
|---|---|
| Dissolution Method | |
| *Apparatus/Speed*<br>*Media/Volume*<br>*Bath temperature* | USP Apparatus 2 (paddle)/35 rpm<br>1000mL of water with 0.3% w/v SLS,<br>37.0±0.5°C |
| Dissolution Acceptance Criterion | |
| NLT (b) (4) %(Q) in 20 minutes | |

From Biopharmaceutics perspective, the NDA 214522 for TADLIQ™ (tadalafil) Oral Suspension, 4 mg/mL was recommended for **APPROVAL**[1] in the original submission.

In the current resubmission, no new dissolution data for the bio-batch or registration batches on long-term or accelerated stability conditions were provided. Additionally, no formulation, manufacturing site or process changes are proposed in the current submission. Hence, no Biopharmaceutics assessment of the dissolution data was performed in the current submission.

***RECOMMENDATION:*** From Biopharmaceutics perspective, the NDA 214522 for TADLIQ™ (tadalafil) Oral Suspension, 4 mg/mL stands **APPROVED** and no additional action is indicated.

[1] Biopharmaceutics review for NDA 214522 for TADLIQ™ (tadalafil) Oral Suspension, 4 mg/mL https://panorama.fda.gov/task/view?ID=5efdf34900544884b9d9c17952d322c1

Parnali Chatterjee

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Haritha Mandula

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/s/

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THEODORE E CARVER
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# NDA 214522

# TADLIQ™ (tadalafil) Oral Suspension

## Integrated Quality Review

### Quality Recommendation: Complete Response

**This is a corrected review of the original NDA submission (Review #1) that does not change the recommendations/conclusions of the Review dated 02/12/2021 or the review and recommendation of the resubmitted NDA resubmission (SD#15, dated 5/27/2022).**

| | |
|---|---|
| Drug Name | TADLIQ™ (tadalafil) oral suspension |
| Indication | Treatment of pulmonary hypertension to improve exercise ability |
| Dosage form | Oral Suspension |
| Strength | 20 mg/5 mL |
| Route of Administration | Oral |
| Rx/OTC Dispensed | Rx |
| Applicant | CMP Develoment, LLC. |
| US agent, if applicable | N/A |
| Submission (s) Reviewed | NDA 214522 original submission and all CMC amendments |

Quality Review Team

| DISCIPLINE | REVIEWER | BRANCH/DIVISION |
|---|---|---|
| Drug Substance | Sithamalli Chandramouli | ONDP/NDABIII |
| Drug Product/Labeling/Environmental Assessment | Theodore Carver | ONDP/ NDPBV |

| | | |
|---|---|---|
| Process and Facility | Kumar Janoria/Vidya Pai | OPMA/DPMAIV/PMB12 |
| Biopharmaceutics | Parnali Chatterjee | ONDP/DB/BB2 |
| Application Team Lead | Theodore Carver | ONDP/ NDPBV |
| Regulatory Business Process Manager | Grafton Adams | OPRO DRBPMI/RBPMBI |

## EXECUTIVE SUMMARY

### 1. Recommendation and Conclusion on Approvability

The Office of Pharmaceutical Quality (OPQ) does not recommend approval of NDA 214522, due to deficiencies identified in the drug product manufacturing and testing facilities.

### 2. Background Summary

The Applicant, CMP Development, Ltd., is seeking U.S. marketing approval for Tadalafil Oral Suspension, 20 mg/5 mL, in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. Tadalafil Oral Suspension is indicated for pulmonary arterial hypertension. For the approval of this NDA, the Applicant relies on FDA's previous finding of safety and efficacy for the listed drug (LD), ADCIRCA® (Tadalafil) tablets, NDA 022332, held by Eli Lilly and Company. In addition, this application contains supporting in vivo bioavailability studies. The proposed product is a liquid oral formulation that is intended to be easier to administer for patients with difficulty swallowing tablets. In comparison with the listed drug, the route of administration and dose of Tadalafil Oral Suspension are the same as for the reference product, but the formulation and composition are different.

### 3. Summary of Quality Assessment

Tadalafil oral suspension, a new formulation of tadalafil USP, is a white to off-white aqueous suspension to be marketed as a single strength of 20 mg/5mL (4 mg/mL). The drug product contains excipients that contribute to maintaining the quality of the drug product in suspension form during storage and use, including (b) (4) mg/mL glycerin, (b) (4) mg/mL xanthan gum, (b) (4) mg/mL polysorbate 80, and (b) (4) mg/mL simethicone emulsion. In addition, the product is (b) (4) citric acid monohydrate and trisodium citrate dihydrate, with sodium benzoate (b) (4) peppermint flavor (b) (4). The product is packaged in 150 mL (b) (4) bottles with a white plastic cap. No dosing device is co-packaged with the drug product. The manufacturing of the drug substance, the specifications, and supporting stability data for the drug product were found to be adequate. However, the drug product manufacturing and testing facilities, (b) (4) have unresolved facility deficiencies resulting in a Withhold

status, requiring on-site inspections after resolution of these deficiencies. Additional non-approvability issues were also noted during review of the drug product manufacturing process.

### 3.1. Drug Substance (Tadalafil)

The tadalafil drug substance was reviewed by Dr. Sithamalli Chandramouli and found to be adequate. The drug substance, tadalafil USP, Pyrazino [1', 2':1, 6] pyrido [3, 4-b] indole-1, 4-dione, 6-(1, 3-benzodioxol-5-yl)-2, 3, 6, 7, 12, 12a-hexahydro-2-methyl-(6R, 12aR), is referenced to DMF (b) (4) for chemistry, manufacturing, and controls information. This DMF has been reviewed and remains adequate to support this NDA (review No. 8, 2020). The drug substance conforms to the USP monograph for tadalafil, USP. Specified enantiomeric and diastereomeric impurities listed in the USP monograph are adequately characterized and controlled in the drug substance. In addition, a process-related impurity, termed the (b) (4) impurity' is included in the specification and controlled at a level of (b) (4) ppm, which does not exceed the ICH daily exposure limit of 1.5 mcg. per day. Elemental impurities are controlled adequately based on information from the DMF holder in the NDA. Residual solvents are also controlled appropriately in the drug substance based on ICH Q3C. The stability data in the DMF support a retest date of (b) (4) months for the drug substance. Particle size and polymorphic form of the drugs substance that are critical quality attributes of the (b) (4) with respect to dissolution and stability of the drug product, and tests for particle size and polymorphic form are included in the drug substance specification.

### 3.2. Drug Product (Tadalafil oral suspension)

**A) Product Design and Specifications:** The drug product is an aqueous suspension intended for oral administration at a single strength of 20 mg/5 mL (4 mg/mL). Dr. Theodore Carver performed the review of the drug product. The tadalafil oral suspension was developed as an alternative oral dosage form for patients with dysphagia (difficulty swallowing). The recommended daily dose for TADLIQ™ (tadalafil) Oral Suspension is 40 mg (10 mL) to be taken once daily with or without food. Since the tadalafil drug substance is practically insoluble in water, the drug product is manufactured as a liquid suspension of tadalafil with (b) (4) excipients. Critical quality attributes of the drug product include particle size, suspension uniformity, palatability, microbiological properties, and stability, which were evaluated as part of the (b) (4) . In terms of composition, the drug product contains 4 mg/mL tadalafil (USP) as the active ingredient, (b) (4) mg /mL sodium benzoate (NF) (b) (4) (b) (4) mg/mL xanthan gum (NF) (b) (4) (b) (4) mg/mL sucrose (NF) (b) (4) (b) (4) mg/mL glycerin (USP) (b) (4) (b) (4) mg/ mL citric acid monohydrate (USP) (b) (4) (b) (4) mg/mL trisodium citrate dihydrate (USP) (b) (4) (b) (4) polysorbate 80 (NF) as a (b) (4) (b) (4) mg/mL 30% simethicone emulsion (USP) (b) (4), and (b) (4) mg/mL (b) (4) peppermint flavor (referenced to DMF (b) (4)) (b) (4) these (b) (4) . All of the ingredients are compendial except for the (b) (4) peppermint flavor, for which additional manufacturing information was provided to support its safe use. The Applicant conducted development studies to optimize the formulation with respect to critical quality attributes of the drug product including API particle size, excipient

concentrations and compatibility, pH, viscosity, sedimentation volume, dissolution, and stability. The container closure system consists of 150 mL (b) (4) bottles with white (b) (4) (b) (4) caps (b) (4). The applicant performed a limited extraction study confirming that no leachables are generated from the container closure system. The drug product specification includes appropriate tests and acceptance criteria with respect to the identity, potency, and purity of the drug product based on its Quality Target Product Profile (QTPP), including viscosity, resuspendability, and suspension testing to confirm that the oral suspension retains the physicochemical attributes required for correct dosing both at release and during storage. The drug product is resuspended by shaking the bottle before each use, and the shaking time specified in the labeling (30 seconds) is supported by release and stability data submitted to the NDA. Stability data were provided supporting a shelf life of 24 months storage at 20°C to 25 °C.

**B) Drug Product Manufacturing**: Tadalafil oral suspension is manufactured by (b) (4)

(b) (4)

**C) Biopharmaceutics Aspects:** The proposed drug product is a suspension of tadalafil, which is a crystalline (b) (4) racemic drug substance with low aqueous solubility (0.01 mg/mL) in buffer solutions across the physiological pH range, pH 1.2 to 6.8. Dr. Parnali Chatterjee performed the biopharmaceutics review, with the objective of evaluating the dissolution profile data, the proposed dissolution method, acceptance criteria, and impact of any changes due to manufacturing site, process, or formulation changes for TADLIQ™ (tadalafil) Oral Suspension, 4 mg/mL. No changes presenting a risk to dissolution and release of the drug product were noted for the clinical and commercial manufacturing processes. The dissolution acceptance criterion for the commercial product is set at *'NLT* (b) (4) *% (Q) in 20 minutes'* to ensure rapid and almost complete release of the drug product within 20 minutes. The overall dissolution data provided for the clinical and registration batches at release, on stability, and

to support the discriminating ability of the method indicate that this dissolution method is adequate for the testing of 5 mL (20 mg) samples of the proposed drug product.

**D) Microbiological Aspects:** Tadalafil oral suspension is a non-sterile, multi-use drug product for oral administration. (b) (4) is included in the formulation (b) (4) Dr. Denise Miller performed the quality microbiology review with a focus on (b) (4) effectiveness and microbiological release testing to address microbiological risks for the drug product. A hold time study supports the microbial quality of the bulk product when held in (b) (4). Antimicrobial effectiveness testing for three lots of drug product support the effectiveness of the (b) (4) in providing microbial control at the proposed concentration (NLT (b) (4)% of the label claim). Microbiological test methods and acceptance criteria included in the drug product release specification are adequate. The ability of the (b) (4) to control microbial quality over the shelf life will be established in stability studies as part of the post-approval stability committment.

**E) Container Closure System:** The drug product is (b) (4) (b) (4) studies and is packaged in a suitably (b) (4) container closure system, amber bottles with (b) (4) caps. The total volume of the bottle is (b) (4) with a 150 mL fill volume.

4. **Assessment of Manufacturing Facilities:** The overall manufacturing inspection recommendation (OMIR) from the Office of Process Manufacturing Assessment (OPMA) for this NDA is to withhold approval. Facility compliance information for the drug substance and drug product were reviewed by Dr. Vidya Pai. This review concluded that all facilities associated with this application are acceptable except for two facilities, as shown in the table below: the drug product manufacturing facility, (b) (4)

(b) (4), the drug product manufacturing facility, has no prior inspection history, and a 704(a)(4) records review of another NDA for a similar dosage form was performed, based on the results of a partner inspection (MHRA). The records review resulted in a withhold recommendation for (b) (4) for this facility, due to issues identified in the (b) (4) for which responses to information requests were reviewed through (b) (4) and found to be deficient. This facility has a withhold recommendation, and a satisfactory on-site inspection of this facility will be required prior to NDA approval.

(b) (4)

recent GMP inspection, conducted from (b) (4), resulted in an OAI, with deficiencies related to a failure to follow laboratory controls and an inadequate number of qualified personnel. This facility is currently out-of-compliance with respect to cGMP and has a withhold recommendation.

| Facility name and address | FEI | Responsibilities | Status |
|---|---|---|---|
| (b) (4) | | | **Withhold based on deficient 704(a)(4)** |
| | | | Approve - Based on Previous History |
| | | | **Withhold based on cGMP** |
| | | | No Evaluation Necessary |
| CMP Pharma, Inc.<br><br>8026 US Highway 264A , Farmville, North Carolina, USA, 27828 | 1050589 | Labeling Operations of Drug Product | Approve - Based on Previous History |

5. **Expiration Date & Storage Conditions:** The Applicant proposes a 24-month shelf life based on 12 months long-term and 6 months accelerated stability data, for 3 batches manufactured at the (b) (4) commercial scale. No trending or anomalous results were observed for any test on stability, for any storage condition. Based on available stability data, an expiration period of 24 months is granted when stored at 20°C to 25°C (68°F to 77°F) in commercial packaging, with excursions permitted to 15°C to 30°C (59°F to 86°F).

6. **Environmental Assessment:** The Applicant requested a Categorical Exclusion [21 CFR 314.50 (d) (l) (iii)] in that this drug product will not be administered at higher dosage levels, for longer duration, or for different indications than were previously in effect. The Applicant stated that, to the Applicant's knowledge, no extraordinary circumstances exist. This claim is acceptable for this 505(b)(2) application.

7. **Quality Labeling**: The container and carton label were reviewed as part of the drug product review. The dosage form description, strength, established name, NDC #, Lot #/Expiry, and storage conditions are adequately described in the carton and container label, which meets relevant regulatory requirements for labeling. Refer to the labeling review for additional information.

8. **List of CMC Deficiencies:**

Facility Deficiencies:

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. These objectionable conditions will be conveyed to the representative of the facility within 10 business days of this Complete Response Letter. Satisfactory resolution of these objectionable conditions is required (e.g., preapproval inspection and/or adequate facility responses addressing these conditions) before this application may be approved.

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

   For more information, please see FDA guidances related to COVID 19. These guidances can be found at

   https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders

2. During a recent inspection of the (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.

9. **Additional Comments for Action Letter:**

Drug Product:

(b) (4)

**OVERALL ASSESSMENT AND FINAL RECOMMNDATION**

**Application Technical Lead (ATL) Assessment and Signature:**

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 214522 (tadalafil oral suspension) was **not** recommended for approval as of 2/12/2021. (This is a corrected version of an earlier review and does not reflect the conclusion as of the signature date).

Theodore Carver, Ph.D.

Application Technical Lead (ATL)
Review Chemist
ONDP/DNDPI/NDPBV

## Life Cycle Knowledge Management

## Final Risk Assessment: NDA 214522

## TADLIQ™ (tadalafil) Oral Suspension

| Product Property/ *CQAs* | Factors that can Impact the CQAs | Initial Risk Ranking | Risk Mitigation Approach | Final Risk Evaluation | Comment |
|---|---|---|---|---|---|
| Assay, Stability | • Formulation<br>• Container closure<br>• Raw materials<br>• Process parameters<br>• Scale/equipment/ site | Medium | (b) (4) | **Not Acceptable. Basis for a CR recommendation.** | Facilities for drug product manufacturing and testing currently have withhold recommendations. |
| Physical stability (suspension) | • Formulation<br>• Raw materials<br>• Process parameters<br>• Scale/equipment/ site | Medium | | **Not Acceptable. Basis for a CR recommendation.** | Facilities for drug product manufacturing and testing currently have withhold recommendations. |
| Dosing Accuracy | • Formulation<br>• Raw materials<br>• Process parameters for mixing | Low | | **Acceptable** | (b) (4) |
| pH | • Formulation<br>• Raw materials<br>• Process parameters<br>• in-process controls | Low | | **Acceptable** | |

| | | | | | |
|---|---|---|---|---|---|
| Microbiological quality | • Formulation<br>• Raw materials<br>• Preservative content | Low | | **Acceptable** | |
| Palatability | • Formulation<br>• Excipient selection<br>• Process parameters<br>• Scale/equipment/ site | Low | | **Acceptable** | |
| Dissolution | • Formulation<br>• Raw materials<br>• Process parameters<br>• Scale/equipment/ site | Low | | **Not Acceptable. Basis for a CR recommendation.** | Facility for drug product testing currently has a withhold recommendation. |
| Leachables | • Formulation<br>• Container closure | | | **Acceptable** | Formulation is similar to an oral aqueous formulation. |

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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:** ***Adequate with revisions as noted below.***

### 1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| **Product Title in Highlights** | | |
| Proprietary name | TADLIQ® (tadalafil (b) (4)) | Adequate |
| Established name(s) | | Adequate. A labeling comment was sent to Applicant regarding the choice of name in parentheses. May be revised to TADLIQ® (tadalafil) by the Applicant. |
| Route(s) of administration | | Adequate. |
| **Dosage Forms and Strengths Heading in Highlights** | | |
| Summary of the dosage form(s) and strength(s) in metric system. | Oral Suspension: (b) (4) | Inadequate. Change to 20 mg/5 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 | | N/A |

| | | |
|---|---|---|
| pharmacy bulk package and imaging bulk package. | | |

## 1.2 FULL PRESCRIBING INFORMATION

### 1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

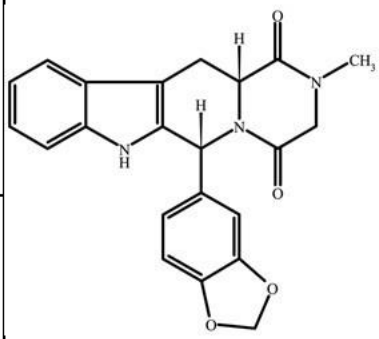
| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| **DOSAGE AND ADMINISTRATION section** | | |

| | | |
|---|---|---|
| Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product) | **2.1 Pulmonary Arterial Hypertension**<br>The recommended dose of TADLIQ is 40 mg (10 mL) taken once daily with or without food. (b) (4)<br><br>**2.2** (b) (4)<br><br><u>Renal Impairment</u><br>• Mild (creatinine clearance 51 to 80 mL/min) or moderate (creatinine clearance 31 to 50 mL/min): Start dosing at 20 mg (5 mL) once daily. Increase to 40 mg (10 mL) once daily based on individual tolerability.<br>• Severe (creatinine clearance <30 mL/min and on hemodialysis): Avoid use of TADLIQ because of increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis *[see* (b) (4) *Use in Specific Populations (8.6)].*<br><br><u>Hepatic Impairment</u><br>• Mild or moderate (Child Pugh Class A or B): Because of limited clinical experience in patients with mild to moderate hepatic cirrhosis, consider a starting dose of 20 mg (5 mL) once per day.<br>• Severe (Child Pugh Class C): Patients with severe hepatic cirrhosis have not been studied. Avoid use of TADLIQ *[see* (b) (4) *Use in Specific Populations (8.7)].*<br><br>(b) (4)<br><br>**2(b) Use with Ritonavir**<br><u>Co-administration of TADLIQ in Patients on Ritonavir</u><br>In patients receiving ritonavir for at least one week, start TADLIQ at 20 mg (5 mL) once daily. Increase to 40 mg (10 mL) once daily based upon individual tolerability *[see* (b) (4) *Drug Interactions (7* (b) (4) *and Clinical Pharmacology (12.3)].*<br><br><u>Co-administration of Ritonavir in Patients on TADLIQ</u><br>Avoid use of TADLIQ during the initiation of ritonavir. Stop TADLIQ at least 24 hours prior to starting ritonavir. After at least one week following the initiation of ritonavir, resume TADLIQ at 20 mg (5 mL) once daily. Increase to 40 mg (10 mL) once daily based upon individual tolerability *[see* (b) (4) *Drug Interactions (7* (b) (4) *and Clinical Pharmacology (12.3)].* | Adequate – however, patient instructions should include the instruction to shake the bottle for 30 seconds before use (see below). This shaking time has been confirmed as adequate for resuspension by the Applicant. |

## 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: (b) (4) ; white to off-white opaque suspension with a peppermint flavor. | Adequate. |
| Strength(s) in metric system | | Adequate |
| If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance | | N/A; active ingredient is not a salt. |
| A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting | | Adequate. |
| 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 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 |

### 1.2.3 Section 11 (DESCRIPTION)

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| **DESCRIPTION section** | | |
| Proprietary and established name(s) | TADLIQ, an oral (b) (4) (b) (4) is a selective inhibitor of cyclic guanosine monophosphate (cGMP)–specific phosphodiesterase type 5 (PDE5). Tadalafil has the empirical formula $C_{22}H_{19}N_3O_4$ representing a molecular weight of 389.41. The structural formula is:  The chemical designation is pyrazino[1´,2´:1,6]pyrido[3,4–b]indole-1,4-dione, 6-(1,3-benzodioxol-5- yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)-. It is a crystalline solid that is practically insoluble in water and very slightly soluble in ethanol. TADLIQ oral suspension contains (b) (4) of tadalafil and the following inactive ingredients: 30% simethicone emulsion, citric acid monohydrate, glycerin, peppermint flavor, polysorbate 80, purified water, sodium | Adequate |
| Dosage form(s) and route(s) of administration | | Adequate. |
| If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance. | | Adequate. The active ingredient is not a salt. |
| List names of all inactive ingredients. Use USP/NF names. Avoid Brand names. | | Adequate. |
| 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 |
| Statement of being sterile (if applicable) | | N/A |
| Pharmacological/ therapeutic class | | Inadequate. Remove the reference to the (b) (4) |

| | | |
|---|---|---|
| | benzoate, sucralose powder, trisodium citrate dihydrate, xanthan gum. | |
| Chemical name, structural formula, molecular weight | See above | Adequate |
| If radioactive, statement of important nuclear characteristics. | | N/A |
| Other important chemical or physical properties (such as pKa or pH) | | Adequate. |

**Section 11 (DESCRIPTION) Continued**

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| For oral prescription drug products, include gluten statement if applicable | None. | N/A |
| Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity" | None. | Adequate. |

### 1.2.4 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) | TADLIQ (tadalafil) Oral Suspension, [redacted] (b) (4) is a white to off-white, opaque, peppermint-flavored suspension. It is available in a 150 mL bottle (NDC 46287-045-15)<br>**16.1 Storage**<br>Store at 25°C (77°F): excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Shake well for 30 seconds before use. Dispense in a tight container as defined in the USP.<br>Keep out of reach of children. | Inadequate. Change the highlighted to "Store at 20°C to 25°C (68°F to 77°F):" |
| Strength(s) in metric system | | Adequate. |
| Available units (e.g., bottles of 100 tablets) | | Adequate. |
| Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number | | Adequate. The product description corresponds to an oral suspension. |
| Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored" | N/A | N/A |

| | | |
|---|---|---|
| For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use).<br>Other package terms include pharmacy bulk package and imaging bulk package. | N/A | N/A |

**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.) | | Inadequate. The highlighted text does not provide instructions for administering the product. The Applicant indicated in the response to an IR that (b) (4) [redacted] |
| If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat." | N/A | N/A |
| Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. | See above. | Revise highlighted storage condition to include the temperature range as in the container label, which are supported |

| | | |
|---|---|---|
| | | by the stability data in the application, i.e.: "Store at 20-25°C (77°F): excursions permitted to 15–30°C (59–86°F) [see USP 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: "Not made with natural rubber latex. Avoid statements such as "latex-free." | No information included. | N/A |
| Include information about child-resistant packaging | No Information included. | Includes statement "Keep out of reach of children". |

### 1.2.5 Other Sections of Labeling

N/A

### *1.2.6* 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:<br>CMP Pharma, Inc.<br><br>8026 US Highway 264A, Farmville, NC 27828 | Adequate. Includes information for the U.S. distributor. |

## 2.0 PATIENT LABELING

**Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):**
We recommend that the Patient Information included in the prescribing information include instructions to shake the bottle well for 30 seconds before each use. This was included in the proposed labeling revisions (12/11/20).

## 3.0 CARTON AND CONTAINER LABELING

**Assessment of Container and Carton labeling: The following changes should be made to the carton labeling:**

- The size of the lettering in the established name should be increased so that it is no less than ½ the height of the lettering in the proprietary name.
- Instructions for shaking well for 30 seconds before use should be included here.

### 3.1 Container Label

(b) (4)

### 3.2 Carton Labeling

N/A

## ITEMS FOR ADDITIONAL ASSESSMENT

**N/A**

***Overall Assessment and Recommendation:***

The labeling/labels will be adequate from a quality perspective after the recommended changes have been made.

David Claffey

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Theodore Carver

Digitally signed by Theodore Carver
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# CHAPTER VII: MICROBIOLOGY

| | |
|---|---|
| **Product Information** | This is a liquid oral suspension drug product for the treatment of pulmonary arterial hypertension to improve exercise ability. |
| **NDA Number** | 214-522 |
| **Assessment Cycle Number** | 1 |
| **Drug Product Name/ Strength** | Tadliq (Tadalafil Oral Suspension) 4 mg/mL |
| **Route of Administration** | Oral |
| **Applicant Name** | CMP Development LLC |
| **Therapeutic Classification/ OND Division** | CDER/OND/ODEI/DCRP |
| **Manufacturing Site** | (b) (4) |
| **Method of Sterilization** | NA, not required to be sterile |

***Assessment Recommendation:*** **Adequate**

***Assessment Summary:*** As this is a non-sterile (b) (4) drug product for oral administration, the quality microbiology review concentrated on (b) (4) effectiveness and microbial release testing.

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

| Document(s) Assessed | Date Received |
|---|---|
| **Original NDA** | **04/23/2020** |

**Highlight Key Issues from Last Cycle and Their Resolution: NA**

**Remarks: NA**

**Concise Description of Outstanding Issues**
**(List bullet points with key information and update as needed): NA**

**Supporting Documents: NA**

**S DRUG SUBSTANCE: NA,** Drug substance is not sterile.

## P DRUG PRODUCT

## P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Tadalafil Oral Suspension is a non-sterile preserved white to off-white suspension with a peppermint flavor. It is a multi-use product supplied in a 150 mL (b) (4) The composition below is copied from submission Table 1 of section 3.2.P.3.2 Batch Formula:

**Table 1: Theoretical Qualitative and Quantitative Composition and Batch Formula**

| Ingredient | Quality Standard | Function | % w/v | Quantity/mL (mg/mL) | Exhibit Batch (b) (4) | Proposed Commercial Batch (b) (4) | (b) (4) |
|---|---|---|---|---|---|---|---|
| Tadalafil[1] | USP | API | (b) (4) | 4.00 | (b) (4) | (b) (4) | (b) (4) |
| Sodium Benzoate | NF | (b) (4) | | (b) (4) | | | |
| Xanthan Gum (b) (4) | NF | | | | | | |
| Sucralose | NF | | | | | | |
| Glycerin | USP | | | | | | |
| Citric Acid Monohydrate | USP | | | | | | |
| Tri-Sodium Citrate Dihydrate | USP | | | | | | |
| Polysorbate 80 (b) (4) | NF | | | | | | |
| 30% Simethicone Emulsion | USP | | | | | | |
| (b) (4) Peppermint Flavor (b) (4) | N/A | | | | | | |
| Purified Water | USP | | | | | | |
| **Total** | | | 100.00% | | | | |

**Assessment: *Adequate***

## P.2 PHARMACEUTICAL DEVELOPMENT

## P.2.5 MICROBIOLOGICAL ATTRIBUTES

Container/Closure and Package Integrity: NA

**Assessment: NA**

(b) (4)

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**MICROBIOLOGY LIST OF DEFICIENCIES: NA**

No deficiencies identified.

*Primary Microbiology Assessor Name: Denise Miller*
*Sr. Microbiologist, OPQ/OPMA/DMA/MAB5*
*Secondary Assessor Name: Bryan Riley Ph.D.*
*Branch Chief, OPQ/OPMA/DMA/MAB5*

Denise Miller

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Bryan Riley

Digitally signed by Bryan Riley
Date: 7/16/2020 11:09:16AM
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# BIOPHARMACEUTICS

**NDA:** 214522-ORIG-1
**Drug Product Name / Strength:** TADLIQ™ (tadalafil) Oral Suspension, 4 mg/mL
**Route of Administration:** Oral
**Applicant Name:** CMP Development, LLC
**Primary Reviewer:** Parnali Chatterjee, Ph.D.
**Secondary Reviewer:**.Poonam Delvadia, Ph.D.

## *EXECUTIVE SUMMARY:*

***Background:*** CMP Development, LLC is seeking approval of TADLIQ™ (tadalafil) Oral Suspension, 4 mg/mL for the treatment of pulmonary arterial hypertension (PAH) to improve exercise ability *via* the 505 (b)(2) regulatory pathway. The submission references ADCIRCA™, 20 mg [NDA 022332, Approved on 05/22/2009] as the Listed Drug (LD) for pharmacokinetic bridge to the proposed drug product. The recommended daily dose for TADLIQ™ (tadalafil) Oral Suspension is 40 mg (10 mL) to be taken once daily with or without food.

The NDA is supported by a comparative open-label, randomized, single-dose, two treatment, three sequence, three period, crossover bioequivalence (BE) study 19-016 conducted with 5 mL (equivalent to 20 mg tadalafil) of the proposed drug product batch VAL/18/0103 and 20 mg tablet of the LD in healthy, adult, human subjects under fasting and fed conditions to provide a pharmacokinetic bridge. The NDA is also relying on the FDA's findings of safety and efficacy studies conducted with the LD, ADCIRCA™, 20 mg.

## ***REVIEW SUMMARY:***

The objective of this Biopharmaceutics Review is to evaluate the overall dissolution profile data and provide recommendations for **1)** the proposed dissolution method, **2)** the proposed dissolution acceptance criterion, and 3) '*bridging*' of drug products due to manufacturing site, process, or formulation changes for TADLIQ™ (tadalafil) Oral Suspension, 4 mg/mL.

- ***Proposed Dissolution Method:***

The Applicant provided dissolution profile data with 5 mL (20 mg) of the drug product in support of the following quality control (QC) dissolution method for dissolution testing of the proposed drug product:

| Parameters | Originally Proposed Dissolution Method |
|---|---|
| *Apparatus/Speed* | USP Apparatus 2 (paddle) (b)(4) rpm |
| *Media/Volume* | 1000mL of water with (b)(4)% w/v SLS, |
| *Bath temperature* | 37.0±0.5°C |

The overall dissolution data for the clinical and registration batches of the drug product at batch release demonstrated (b) (4) The dissolution data supported (b) (4) in the dissolution media. Based on the FDA's recommendations, the Applicant proposed a new quality control dissolution method for the proposed drug product as follows:

| Parameters | **Newly Proposed and ACCEPTABLE** Dissolution Method |
|---|---|
| *Apparatus/Speed* | USP Apparatus 2 (paddle)/35 rpm |
| *Media/Volume* | 1000mL of water with 0.3% w/v SLS, |
| *Bath temperature* | 37.0±0.5°C |

The dissolution data for batches at release and on long-term stability for approximately 23 months support the newly proposed dissolution method. The Applicant provided dissolution data that supports limited discriminating ability of the newly proposed dissolution method (b) (4)

The overall dissolution data provided for the clinical and registration batches at release, on stability, and to support the discriminating ability of the dissolution method indicates the newly proposed dissolution method is limited with respect to dissolution testing of 5 mL (20 mg) of the proposed drug product:

It should be noted that the new dissolution method (b) (4)

- ***Dissolution Acceptance Criterion***:

The Applicant proposed '*NLT* (b) (4) *% (Q) in* (b) (4) *minutes'* as the dissolution acceptance criterion for quality control of TADLIQ™ (tadalafil) Oral Suspension, 4 mg/mL drug product at batch release and on stability. The overall dissolution data for the clinical and registration batches of the drug product at batch release support '*NLT* (b) (4) *% (Q) in 20 minutes'* as the acceptance criterion for the proposed drug product that the Applicant agreed to implement for the proposed drug product on FDA's recommendations.

| | Dissolution Acceptance Criterion |
|---|---|
| Proposed | *NLT* (b) (4) *% (Q) in* (b) (4) *minutes* |
| **Approved** | ***NLT*** (b) (4) ***%(Q) in 20 minutes*** |

- ***Bridging of Drug Product Batches due to Manufacturing Site, Process, or Formulation Changes***:

As the clinical trial, registration, and commercial batches are manufactured at the same manufacturing site, and there are no manufacturing process or formulation changes between the clinical and commercial batches, no '*bridging*' of batches is necessary.

- ***BIOPHARMACEUTICS RISK ASSESSMENT:***

Tadalafil is a crystalline (b) (4) racemic drug substance that demonstrates pH-independent, rate-limiting, low aqueous solubility (0.01 mg/mL) in buffer solutions across the physiological pH range 1.2-6.8. (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4) Additional CMC information and other critical quality controls that are part of the risk mitigation, will be evaluated and addressed by the CMC Reviewer(s).

***OVERALL REVIEW RECOMMENDATION:***

From Biopharmaceutics perspective, the NDA 214522 for TADLIQ™ (tadalafil) Oral Suspension, 4 mg/mL is recommended for **APPROVAL.**

## BIOPHARMACEUTICS ASSESSMENT

- **LIST OF SUBMISSIONS BEING REVIEWED:**

| Submissions Reviewed | Reference ID |
|---|---|
| Original NDA 214522 Submission | Dated 04/23/2020, SDN 1 (\\CDSESUB1\evsprod\nda214522\0000\m2\27-clin-sum\271-summary-biopharm.pdf) |
| Response to Information Request #1 | Dated 08/03/2020, SDN 5 (\\CDSESUB1\evsprod\nda214522\0004\m1\us\1-2-cover-letters\1-2-2-cover-letters.pdf) |
| Response to Information Request #2 | Dated 09/08/2020, SDN 8 (\\CDSESUB1\evsprod\nda214522\0007\m1\us\1-2-cover-letters\1-2-2-cover-letters.pdf) |
| Response to Information Request #3 | Dated 10/27/2020, SDN 10 (\\CDSESUB1\evsprod\nda214522\0009\m3\32-body-data\32p-drug-prod\tadalafil-os\32p2-pharm-dev\32p2-3-comp-disso-study-rep.pdf) |
| Response to Information Request #4 | Dated 11/18/2020, SDN 11 (\\CDSESUB1\evsprod\nda214522\0010\m1\us\1-2-cover-letters\1-2-2-cover-letters.pdf) |

- ***DRUG SUBSTANCE*:**

The proposed drug product contains tadalafil [molecular formula: $C_{22}H_{19}N_3O_4$; molecular weight=389.4 grams/mole], a white, crystalline (b) (4), non-hygroscopic, racemic drug substance. The Applicant referenced the DMF (b) (4) for (b) (4) The biophysico-chemical properties of the drug substance are provided below:

- ***Solubility:***

The equilibrium solubility of tadalafil in buffer solutions across the physiological pH range 1.2-6.8 at 25 C±2 C is 1 mg/100 mL (see **Table 1**); indicating tadalafil is a low soluble drug substance. The highest recommended daily dose of the drug substance (i.e., 40 mg) in the drug product will not be soluble in 250 mL buffer solutions across the physiological pH range (b) (4) Therefore, tadalafil is a low aqueous soluble drug substance per Biopharmaceutics Classification System (BCS).

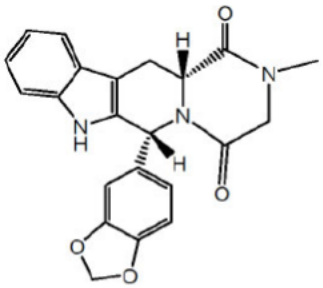
**Table 1**. Equilibrium solubility of tadalafil in buffer solutions across the physiological pH range 1.2-6.8 at 25 C±2 C

| S.No. | pH | Solubility |
|---|---|---|
| 1 | 1.2 | Insoluble (1 mg/100 mL) |
| 2 | 3.0 | Insoluble (1 mg/100 mL) |
| 3 | 4.5 | Insoluble (1 mg/100 mL) |
| 4 | 6.8 | Insoluble (1 mg/100 mL) |
| 5 | 7.2 | Insoluble (1 mg/100 mL) |
| 6 | 8.0 | Insoluble (1 mg/100 mL) |

- ***Permeability/Absorption:***

The LogD of tadalafil was experimentally determined to be 1.5 (at pH 7.4).

**Figure 1**. Chemical structure of tadalafil



According to literature reports, following oral administration of ADCIRCA™, 20 mg once daily for 10 days, tadalafil is slowly absorbed with mean time to maximum concentration (Tmax) at ~2 hours (median 4 hours) and a Cmax of 378 µg/mL. Tadalafil exhibits linear, dose-proportional pharmacokinetics in healthy subjects when administered a single oral dose of 2.5-20 mg and is eliminated from the body following monoexponential decay with a long half-life of 17.5 hours and a low clearance of 2.48 L/h, indicating that it is extensively bound to plasma proteins (albumin and α1-acid glycoprotein) and tissues. The bioavailability of tadalafil is approximately 80% and is not affected by food. No absolute bioavailability data for tadalafil is available in the literature.

Based on the literature reports, tadalafil demonstrates moderate permeability profile.

- ***Particle Size Distribution (PSD):***

As tadalafil demonstrates low aqueous solubility, the Applicant proposed a suspension drug product and $D_{90}$=NMT (b) (4) µm as a single-tier particle size distribution (PSD) specification for tadalafil drug substance in the proposed drug product.

**Table 2**. Single-tier particle size distribution (PSD) specification for tadalafil drug substance in the proposed drug product

| | | |
|---|---|---|
| Particle Size | | |
| D (0.1) | (b) (4) | For information |
| D (0.5) | | For information |
| D (0.9) | | Not more than (b) (4) µm |

The Applicant proposed the PSD specification for tadalafil drug substance in the proposed drug product based on a study conducted with two different PSD for tadalafil during product development that will discussed in detail under "*Discriminating Ability of the Proposed Dissolution Method*".

***Reviewer's Assessment of Permeability/Absorption:***

Based on the in vivo bioavailability studies, tadalafil can be categorized as a 'moderate' permeability drug substance. From totality of the solubility and permeability data, tadalafil can be classified as a low soluble and moderate permeable BCS Class II drug substance, per Biopharmaceutics Classification System (BCS).

- ***Manufacturing Sites for Drug Substance:***

The Applicant identified (b) (4) as the manufacturer of tadalafil drug substance in the proposed drug product. No other manufacturing site is listed for the proposed drug substance in the current submission.

- ***DRUG PRODUCT*:**

The proposed to-be-marketed (TBM) drug product is a white to off-white suspension containing sodium benzoate, xanthum gum, sucralose, polysorbate 80, and other excipients filled in 150 mL amber bottle (b) (4). The pH of the drug product is maintained between (b) (4) The recommended dose for the proposed product, TADLIQ™ (tadalafil) Oral Suspension, 4 mg/mL is 40 mg/day or 10 mL/day once daily with or without food. (b) (4) .

The composition of the proposed to-be-marketed (TBM) TADLIQ™ (tadalafil) Oral Suspension, 4 mg/mL drug product is provided in **Table 3**.

**Table 3**. Composition of the proposed to-be-marketed TADLIQ™ (tadalafil) Oral Suspension, 4 mg/mL drug product

| Ingredient | Quality Standard | Function | % w/v | Quantity/mL (mg/mL) |
|---|---|---|---|---|
| Tadalafil[1] | USP | API | (b) (4) | 4.00 |
| Sodium Benzoate | NF | (b) (4) | | (b) (4) |
| Xanthan Gum (b) (4) | NF | | | |
| Sucralose | NF | | | |
| Glycerin | USP | | | |
| Citric Acid Monohydrate | USP | | | |
| Tri-Sodium Citrate Dihydrate | USP | | | |
| Polysorbate 80 (b) (4) | NF | | | |
| 30% Simethicone Emulsion | USP | | | |
| (b) (4) Peppermint Flavor (b) (4) | N/A | | | |
| Purified Water | USP | | | |
| **Total** | | | 100.00% | |

- ***Manufacturing Sites for the Proposed Drug Product:***

The product development for the proposed drug product was conducted at (b) (4) The clinical trial batch, scale-up, and registration batches of the proposed drug product were manufactured at (b) (4). The commercial batches will be manufactured at (b) (4) As the clinical trial batches, registration batches, and commercial batches are manufactured at the same manufacturing site, no '*bridging*' of batches is necessary.

- ***DISSOLUTION INFORMATION:***

Dissolution testing was identified as a critical quality attribute (CQA) for the proposed drug product and (b) (4)

- ***DISSOLUTION METHOD:***

(b) (4)



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The overall dissolution data provided for the [redacted] and amount of [redacted] in the drug product can be used to support the discriminating ability of the newly proposed dissolution method ***[USP Apparatus 2 (paddle) at 35 rpm in 1000 mLwater containing 0.3% w/v SLS]***.

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***Reviewer's Assessment of the Proposed Dissolution Method and the Discriminating Ability of the Newly Proposed Dissolution Method:***

The overall dissolution data provided for selection of the dissolution apparatus, agitation speed, pH of the dissolution medium, amount of surfactant in the dissolution medium, and volume of the dissolution medium supports the newly proposed dissolution method*: USP Apparatus 2 in 1000 mL water containing 0.3% w/v SLS at 37°C and at 35 rpm paddle speed* as a quality control method for dissolution testing of 5 mL (20 mg) of the proposed drug product (that was administered in the BE study 19-016).

[redacted]

The newly proposed dissolution method also demonstrated discriminating ability with respect to the amount of [redacted] in the drug product. The overall dissolution data provided to support the proposed dissolution method indicates that the method may not be bio-relevant; though it demonstrates limited discriminating ability and can be used as a quality control method for dissolution testing of 5 mL of the proposed drug product.

However, it should be noted that the newly proposed dissolution method [*USP Apparatus 2 in 1000 mL water containing 0.3% w/v SLS at 37°C and at 35 rpm paddle speed*] [redacted].

- ***PROPOSED DISSOLUTION ACCEPTANCE CRITERION:***

The Applicant proposed '*NLT [redacted]% (Q) in [redacted] minutes*' as the dissolution acceptance criterion for batch release and stability testing of the drug product using the newly proposed dissolution method which is permissive and not acceptable.

***Dissolution Data for the Drug Product Batches using the Newly Proposed Dissolution Method [USP Apparatus 2 (paddle) at 35 rpm in 1000 mL water containing 0.3% w/v SLS]***:

In the original submission, batch release dissolution data at (b) (4) minutes was provided for the clinical and the registration batches. The Applicant was recommended to provide complete batch release dissolution profile data and long-term stability data at the next stability time-point for the clinical and registration batches using the previously proposed dissolution method in an *Information Request* that was communicated to the Applicant on 07/01/2020.

To address the *Information Request* (dated 07/01/2020), the Applicant provided (dated 08/01/2020, SDN 5) complete batch release dissolution profile data and long-term stability data at the next stability time-point for the clinical and registration batches using the previously proposed dissolution method (see: \\CDSESUB1\evsprod\nda214522\0004\m3\32-body-data\32p-drug-prod\tadalafil-os\32p5-contr-drug-prod\32p54-batch-analys\32p54-disso-prof.xlsx) that demonstrate complete dissolution in (b) (4) minutes.

As the dissolution of the drug product was considered (b) (4), on FDA's recommendations the Applicant proposed a new dissolution method using 35 rpm paddle speed and 0.3% w/v SLS in 1000 mL water and provided complete dissolution profile data for 5 mL(20 mg drug product; see **Table 9a**) (b) (4) of the proposed drug product on long-term stability data at approximately 23 months stability time-point for the clinical and registration batches using the newly proposed dissolution method in response (10/27/2020) to the *Information Request* comment.

***Dissolution Data for the Drug Product Batches on Stability using the Newly Proposed Dissolution Method [USP Apparatus 2 (paddle) at 35 rpm in 1000 mLwater containing 0.3% w/v SLS]***:

The dissolution profile data for 5 mL (20 mg) of the clinical and registration batches of the proposed drug product using the newly proposed dissolution method [*USP Apparatus 2 (paddle) at 35 rpm in 1000 mLwater containing 0.3% w/v SLS]* are similar with *f2>50* and would comply with the recommended acceptance criterion of '*NLT* (b) (4) *% (Q) in 20 minutes*' at Stage 1 testing (see **Table 9a**).

(b) (4)

It should be noted that the drug substance demonstrates linear, dose-proportional pharmacokinetics in healthy subjects over the dose range of 2.5-20 mg under fasted condition. The BE study 19-016 was conducted with 5 mL (equivalent to 20 mg tadalafil) of the proposed drug product and 20 mg tablet of the LD,ADCIRCA® in healthy, adult, human subjects. Though the maximum recommended daily dose is 10 mL (~40 mg tadalafil) of the drug product; as the drug substance

demonstrates linearity up to 20 mg (5 mL of the drug product), administration of 10 mL drug product may contribute to non-linear pharmacokinetics. This aspect of dosing falls under the purview of clinical pharmacology reviewer.

**Table 9a**. Mean dissolution profile data for 5 mL (20 mg) of the clinical batch, VAL/18/0103 and registration batches of the proposed drug product using the newly proposed dissolution method [*USP Apparatus 2 (paddle) at 35 rpm in 1000 mL water containing 0.3% w/v SLS at 37°C*] at ~23 months long-term stability time-point

| Time point in | Average % Drug Release | | |
|---|---|---|---|
| | VAL/18/0101 | VAL/18/0102 | VAL/18/0103 |
| 0 minutes | 0 | 0 | 0 |
| 5 minutes | 75 | 71 | 75 |
| 10 minutes | 84 | 81 | 83 |
| 15 minutes | 89 | 85 | 87 |
| 20 minutes | 91 | 88 | 90 |
| 30 minutes | 94 | 92 | 93 |
| 45 minutes | 97 | 94 | 95 |
| 60 minutes | 98 | 96 | 97 |

(b) (4)

- ***IN VIVO BIOAVAILABILITY/BIOEQUIVALENCE STUDY:***

This NDA is supported by a comparative open-label, randomized, single-dose, two treatment, three sequence, three period, crossover bioequivalence (BE) study 19-016 conducted with 5 mL (equivalent to 20 mg tadalafil) of the proposed drug product batch VAL/18/0103 and 20 mg tablet

of the LD (ADCIRCA® [NDA 022332, Approved on 05/22/2009] in healthy, adult, human subjects under fasting and fed conditions to provide the pharmacokinetic bridge.

The geometric least square means ratio of $C_{max}$ (ng/mL) and AUC $_{0\text{-}72\ h}$ (ng*hr/mL) for the proposed drug product batch VAL/18/0103 and 20 mg tablet of the LD under fasted state is 0.94 and 0.98, respectively (see **Table 10a**). The 90% confidence interval (CI) for $C_{max}$ (ng/mL) and AUC $_{0\text{-}72\ h}$ (ng*hr/mL) between the proposed drug product batch VAL/18/0103 and 20 mg tablet of the LD is 88.9-110.2% and 93.5-103.2%, respectively.

**Table 10a**. Geometric least square means ratio, and 90% confidence intervals of the pharmacokinetic parameters for 5 mL (20 mg) of the clinical batch, VAL/18/0103 of the proposed TADLIQ™ (tadalafil) Oral Suspension, 4 mg/mL drug product and LD, ADCIRCA®, 20 mg tablets in healthy human volunteers under fasted condition in the bioequivalence study 19-016

| Pharmacokinetic Parameters (Units) | Ln- transformed Geometric Least Squares Mean | | | 90% Confidence Interval (Parametric) | |
|---|---|---|---|---|---|
| | Test Product ($T_{fast}$) | Reference Product ($R_{fast}$) | $T_{fast}/R_{fast}$ (%) | Lower | Upper |
| $C_{max}$ (ng/mL) | 425.9170 | 451.2170 | 94.39 | 88.92 | 100.20 |
| $AUC_{0\text{-}72h}$ (ng.hr/mL) | 12378.6817 | 12602.9037 | 98.22 | 93.50 | 103.18 |

The geometric least square means ratio of $C_{max}$ (ng/mL) and AUC $_{0\text{-}72\ h}$ (ng*hr/mL) for the proposed drug product batch VAL/18/0103 and 20 mg tablet of the LD under fed state is higher, 1.04 and 1.13, respectively (see **Table 10b**). The 90% confidence interval for $C_{max}$ (ng/mL) and AUC $_{0\text{-}72\ h}$ (ng*hr/mL) between the proposed drug product batch VAL/18/0103 and 20 mg tablet of the LD is 96.5-112.9% and 105.8-120.6%, respectively.

**Table 10b**. Geometric least square means ratio, and 90% confidence intervals of the pharmacokinetic parameters for 5 mL (20 mg) of the clinical batch, VAL/18/0103 of the proposed TADLIQ™ (tadalafil) Oral Suspension, 4 mg/mL drug product and LD, ADCIRCA®, 20 mg tablets in healthy human volunteers under fed condition in the bioequivalence study 19-016

| Pharmacokinetic Parameters (Units) | Ln- transformed Geometric Least Squares Mean | | | 90% Confidence Interval (Parametric) | |
|---|---|---|---|---|---|
| | Test Product ($T_{fed}$) | Test Product ($T_{fast}$) | $T_{fed}/T_{fast}$ (%) | Lower | Upper |
| $C_{max}$ (ng/mL) | 451.6688 | 432.9254 | 104.33 | 96.45 | 112.85 |
| $AUC_{0\text{-}72h}$ (ng.hr/mL) | 14207.7051 | 12579.7334 | 112.94 | 105.78 | 120.59 |

- ***Reviewer's Assessment of the Bioequivalence (BE) Study 19-016 :***

The 90% CI for the ratios of the geometric means for $C_{max}$ (ng/mL) and $AUC_{0\text{-}72\ hours}$ (ng*hr/mL) between 20 mg (5 mL) of the proposed drug product and 20 mg tablets of the LD is within 80%-

125% range under fasted condition and would be considered bioequivalent (see **Table 10a**). The 90% CI for the ratios of the geometric means for $C_{max}$ (ng/mL) and $AUC_{0\text{-}72\ hours}$ (ng*hr/mL) between 20 mg (5 mL) of the proposed drug product and 20 mg tablets of the LD are slightly higher under fed condition; though they are within 80%-125% range and would be considered bioequivalent (see **Table 10b**). The approvability of the BE study 19-016 will be evaluated by the Clinical Pharmacology Reviewer.

***Reviewer's Assessment of the Proposed Dissolution Acceptance Criterion:***

Dissolution data for the clinical batch, VAL/18/0103 administered in the BE Study 19-016 and the registration batches, VAL/18/0101 and VAL/18/0102 support a dissolution acceptance criterion of *'NLT (b)(4)% (Q) in 20 minutes'* (see **Table 9a**) using the newly proposed dissolution method [*USP Apparatus 2 (paddle) at 35 rpm in 1000 mL water containing 0.3% w/v SLS at 37°C]*.

The recommended dissolution acceptance criterion is also supported by the time at which maximum concentration is reached, Tmax=2 hours (range 0.67-4.50 hours) under fasted condition and Tmax=4.50 hours (range 3.33-12.00 hours) under fed state the proposed drug product achieved in the BE study 19-016, indicating variability in the absorption of the drug product probably due to rate-limiting in vivo dissolution of the drug product.

As tadalafil is a drug substance that demonstrates pH-independent, rate-limiting, low aqueous solubility (0.01 mg/mL) in buffer solutions across the physiological pH range 1.2-6.8, the recommended acceptance criterion of *'NLT (b)(4)% (Q) in 20 minutes'* would ensure rapid and almost complete release of the drug product within 20 minutes.

***POST-APPROVAL COMMITMENTS:*** **None**

- ***OVERALL REVIEW RECOMMENDATION:***

From Biopharmaceutics perspective, the NDA 214522 for TADLIQ™ (tadalafil) Oral Suspension, 4 mg/mL is recommended for **APPROVAL.**

Parnali Chatterjee

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Theodore Carver

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