

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209478Orig1s000

PRODUCT QUALITY REVIEW(S)

Memorandum

To: NDA 209478 Administrative File
From: Wendy I. Wilson-Lee, Ph.D.; Acting Branch Chief, OPQ/ONDP/DNDP1/Branch 1
Date: Wednesday, August 09, 2017
Re: NDA 209478 OPQ IQA Correction Memorandum

The purpose of this memorandum is to correct an error in the executive summary of the Office of Pharmaceutical Quality's Integrated Quality Assessment, finalized and archived on June 30, 2017, for NDA 209478 CAROSPIR (spironolactone) Oral Suspension, 25 mg/5 mL from CMP Pharma. On page 3 of the document, Section A. Product Overview includes the following statement:

***"An approved alternative method of administration** for Aldactone tablets and its generic equivalents is compounding into an oral suspension. The proposed product will provide a ready-made oral suspension for use."*

This statement is erroneous. The currently approved labeling for the referenced listed drug Aldactone (spironolactone) Tablets (NDA 12151, last approved version October 22, 2014 under Supplement 72) does not include language regarding alternative methods of administration. There are no FDA-approved alternative methods of administration for Aldactone (spironolactone) Tablets. Rather, the statement in the OPQ IQA document should read the following:

***"An alternative method of administration common in clinical practice** for Aldactone tablets and its generic equivalents is compounding into an oral suspension."*

The revised statement accurately reflects the currently approved RLD labeling while maintaining the pertinent information relevant to the OPQ review.



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Wilson- Lee

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Recommendation: APPROVAL

**NDA 209478
Review #01**

Drug Name/Dosage Form	Spironolactone Oral Suspension
Strength	25 mg/5 mL (5 mg/mL)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	CMP Pharma
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Amendment	Jun. 23, 2017	Labeling
Amendment	Jun. 15, 2017	Drug Product, Env. Analysis
Amendment	May 26, 2017	Drug Product, Biopharm
Amendment	Apr. 28, 2017	All
Amendment	Feb. 03, 2017	Process
Amendment	Nov. 08, 2016	Labeling
Original	Oct. 04, 2016	All

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Haripada Sarker	Branch I/DNDAPI
Drug Product/Labeling/EA	Thomas Wong	Branch I/DNDPI
Process	Peter Guierri	Branch I/DPAI
Microbiology	Jason God	Branch II/DMA
Facility	Cassandra Abellard	Branch II/DIA
Biopharmaceutics	Kaushal Dave	Branch I/DB
Regulatory Business Process Manager	Dahlia Walters	Branch I/DRBPMI
Application Technical Lead	Wendy I. Wilson-Lee	Branch I/DNDPI
OC Lead	Quallyna Porte	GC Branch II/DDQI/OMQ

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	June 1, 2017	

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	12151	Aldactone Tablets
IND	120929	Spirocholactone Suspension

2. CONSULTS

No consults requested.

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends APPROVAL of Spironolactone Oral Suspension, 25 mg/5 mL (5 mg/mL) under NDA 209478.

II. Summary of Quality Assessments

A. Product Overview

Spironolactone Oral Suspension, 25 mg/5 mL (5 mg/mL) is an antagonist of aldosterone. Spironolactone was initially approved under NDA 12151 on December 30, 1983 as a tablet (Reference Listed Drug: Aldactone Tablets 25 mg, 50 mg, and 100 mg). The oral suspension is designed for patients who have difficulty swallowing tablets (b) (4)

An approved alternative method of administration for Aldactone tablets and its generic equivalents is compounding into an oral suspension. The proposed product will provide a ready-made oral suspension for use. The initial product quality risk assessment identified assay over product shelf-life, palatability, characterization of potential leachables, viscosity, content uniformity, resuspendability, and weight loss as moderate risk quality attributes. Based on our review of the information provided in the submission and in response to our information requests, the overall control strategy adequately controls these moderate risk attributes via monitoring/testing, formulation/product design, and appropriate raw material controls. From the quality perspective, the spironolactone oral suspension quality target product profile (QTPP) is appropriate for the intended use and patient population and the to-be-marketed product meets the QTPP. The submission, as amended, supports commercialization of the product. Spironolactone Oral Suspension is considered a low risk product, from a product quality perspective.

Indication(s) including Intended Patient Population	Heart failure, edema caused by (b) (4) cirrhosis, (b) (4) and hypertension (<i>tentative</i>)
Duration of Treatment	Chronic
Maximum Daily Dose	(b) (4) mg (<i>tentative</i>)
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance

Spironolactone is a synthetic, white or cream-colored powder that is practically insoluble in water, soluble in 96% ethanol, slightly soluble in ether. Spironolactone melts between 198°C and 207°C, with decomposition. Spironolactone is known to exist in the form of at least three modifications. (b) (4)

(b) (4)

The drug substance specification complies with the current USP monograph for Spironolactone and includes all the critical drug substance attributes that affect the manufacturing and quality of the drug product. In addition to the compendial tests, the applicant includes tests for particle size, related substances, heavy metals, residue on ignition, residual solvents, and microbiological tests. The organic impurities in the drug substance are consistent with those specified in the USP monograph and the supplier's specification. The drug substance is (b) (4)

CMP Pharma proposes (b) (4) month retest period for the drug substance.

Drug Product

The drug product is a white to off-white, opaque, banana-flavored, immediate release oral suspension. The oral suspension contains 25 mg of spironolactone in 5 ml and is supplied in a 4 ounce bottle (118 mL) and 16 ounce bottles (473 mL). The oral suspension is stored at 20°C to 25°C (68°F to 77°F). Excursions permitted to 15 °C to 30°C (59°F to 86°F). The available stability data supports the proposed expiry dating of 18 months for the 4 ounce bottle and 24 months for the 16 ounce bottle. Results from a resuspendability study during development demonstrate that the formulation design and recommended labeling instructions (i.e. shake well before using) are adequate to ensure resuspension of particles prior to administration. Extraction and migration studies were conducted with the proposed commercial packaging and showed that the levels of extractables were very low and that no migrating compounds were detected.

Spironolactone has a strong odor and unpleasant aftertaste which may impact patient compliance. The formulation design (b) (4)

(b) (4)

The Applicant evaluated the contribution of (b) (4) from the drug substance, excipients, and drug product and determined that the product complies with (b) (4)

Initial assessment of the weight loss data found a significant weight loss coupled with an increasing trend in assay values for the bottles under all storage conditions tested. The bottles are considered semi-permeable containers so the weight loss is most likely caused by evaporation of water from the formulation. This phenomenon could result in a more concentrated suspension which could lead to overdosing, decreased palatability, or inability to administer accurate dosing due to increased viscosity of the suspension. In response to an inquiry, the Applicant included weight loss testing at release and on stability. This addition of weight loss testing along with the (b) (4) end product testing for viscosity and content uniformity will ensure the product meets the label claim over the shelf life.

Process

(b) (4)

(b) (4)

Facilities

A review of the application and inspectional documents of the facilities responsible for manufacturing Spironolactone Oral Suspension 25mg/5 mL determined that there are no significant outstanding risks for these facilities. No inspections were performed. All facilities were found to be acceptable either based on profile or based on district file review.

Biopharmaceutics

The Biopharmaceutics review for this submission is focused on the evaluation of the data supporting approval of the proposed dissolution method and acceptance criterion for Spironolactone Oral Suspension, 25 mg/5 mL. The Applicant initially studied the dissolution of the proposed product using (b) (4)

(b) (4) the Applicant performed further studies to develop a more suitable dissolution method for their proposed drug product. In the original submission, the Applicant proposed (b) (4); however, we recommended (b) (4) and subsequent study of the discriminating ability of the revised dissolution method. Following the FDA's recommendation, the Applicant (b) (4) and showed that the proposed dissolution method is discriminating towards change in drug particle size. Overall, the revised in vitro dissolution method (*USP Apparatus 2, 25 rpm, 900 mL 0.1 N HCl containing 0.01% Cetrimonium Bromide at 37.0°C ± 0.5°C*) and proposed dissolution acceptance criterion of $Q = \frac{(b)(4)}{(4)}\%$ in 15 minutes are adequate.

Microbiology

The drug product is a (b) (4) non-sterile aqueous liquid for oral administration. (b) (4)

(b) (4) The applicant demonstrated that the control strategy is capable of controlling the microbiological quality of the drug product at release and over the proposed

shelf life. The data support a 30 day in-use period from quality microbiology perspective. The application is recommended for approval.

Environmental Assessment

The applicant requested a Categorical Exclusion [21 CFR 25.31 (a)]. The applicant also stated that to the applicant's knowledge, no extraordinary circumstances exist [21 CFR 25.15(d)].

C. Special Product Quality Labeling Recommendations

None.

D. Final Risk Assessment (see Attachment)



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BIOPHARMACEUTICS	
Application No./Submission Date	NDA 209478, dated October 10, 2016
Applicant Name	CMP Pharma, Inc.
Product Name	Carospir™ (Spironolactone) Oral Suspension, 25 mg/5 mL
Primary Reviewer	Kaushalkumar Dave, Ph.D.
Secondary Reviewer	Angelica Dorantes, Ph.D.
RECOMMENDATION	ADEQUATE

EXECUTIVE SUMMARY

Submission: The Applicant is seeking approval for NDA 209478 for Carospir™ (Spironolactone) Oral Suspension, 25 mg/5 mL, via 505(b)(2) route for the treatment of (b) (4). The listed drug product, Aldactone® (Spironolactone) Oral Tablets, was approved under NDA 12151.

Review: The Biopharmaceutics review for this submission is focused on the evaluation of the data supporting approval of the proposed dissolution method and acceptance criterion for Carospir™ (Spironolactone) Oral Suspension, 25 mg/5 mL.

Assessment: The Applicant initially studied the dissolution of the proposed product, Carospir™ (Spironolactone) Oral Suspension, 25 mg/5 mL, (b) (4). (b) (4), the Applicant performed further studies to develop a more suitable dissolution method for their proposed drug product. In the original submission, the Applicant proposed (b) (4); however, the Applicant was recommended to (b) (4) and to study the discriminating ability of the proposed dissolution method. Following the FDA's recommendation, the Applicant (b) (4) and showed that the proposed dissolution method is discriminating towards change in drug particle size.

Conclusion: Overall, the revised in vitro dissolution method and proposed dissolution acceptance criterion of $Q = \frac{(b)}{(4)}\%$ in 15 minutes are adequate.

Recommendation: The following dissolution method and acceptance criterion are acceptable for the quality control of Carospir™ (Spironolactone) suspension, 25 mg/5 mL at release and on stability.

FDA's Approved Dissolution Method and Acceptance Criterion for Carospir™ (Spironolactone), Oral suspension 25 mg/5 mL	
Apparatus	USP Apparatus 2 (paddle)
Paddle Speed	25 rpm
Volume	900 ml
Medium	0.1N HCl containing 0.01% Cetrimonium Bromide
Temperature	37.0 ± 0.5 C
Acceptance Criterion	Not less than ^(b) ₍₄₎ % (Q) at 15 minutes

From a Biopharmaceutics perspective, NDA 209478 for Carospir™ (Spironolactone) suspension, 25 mg/5 mL, is recommended for **APPROVAL**.

Primary Biopharmaceutics Reviewer Name and Date:

Kaushalkumar Dave, Ph.D. 06/08/2017
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

Secondary Reviewer Name and Date:

I concur with Dr. Dave's Biopharmaceutics assessment and recommendation.

Angelica Dorantes, Ph.D. 06/14/2017
Acting Chief, Biopharmaceutics Branch-1
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

BIOPHARMACEUTICS ASSESSMENT

1. LIST OF SUBMISSIONS REVIEWED

Submissions Reviewed		
eCTD sequence #	Received date	Document
0000	10/04/2016	Original NDA Submission
0009	04/28/2017	Quality/Response to Biopharmaceutics Information Request
0010	05/26/2017	Quality/Response to Biopharmaceutics Information Request

2. DRUG PRODUCT

The proposed drug product, Carospir™ (Spironolactone) Suspension, 25 mg/5 mL, is described as a white to off-white, opaque suspension with a banana odor. The product is prepared by a

(b) (4)

. The composition of the product is presented in Table 1:

Table 1: Composition of Carospir™ (Spironolactone) Suspension, 25 mg/5 mL

Ingredient	Quality Standard	Function	% w/v	Quantity/mL (mg/mL)	Quantity/mL (mg/5 mL)
Spironolactone, (b) (4)	USP	API	0.5000	5.000	25.00
Xanthan Gum	NF	(b) (4)			
Simethicone Emulsion (b) (4)	USP				
Sorbic Acid	NF				
Potassium Sorbate	NF				
Sodium Saccharin	USP				
Citric Acid Anhydrous ¹	USP				
Sodium Citrate Dihydrate ¹	USP				
Magnasweet 110	In-house				
Glycerin	USP				
Banana Flavor (b) (4)	In-house				
Purified Water	USP				

3. BCS DESIGNATION

The Applicant stated that the drug substance belongs to BCS Class II. The Applicant did not request BCS designation for Carospir™ (Spironolactone) Oral Suspension in this application.

Solubility

The Applicant stated that the drug substance, spironolactone, is practically insoluble in water, soluble in 96% ethanol, and slightly soluble in ether; however, no solubility data for the drug substance was provided in the original application. According to the Applicant, spironolactone exists in at least three different polymorphic forms (pharmaceutical development report (Module 3.2.P.2)). However, (b) (4)

The proposed product used (b) (4). The Applicant stated that the drug particle size is a critical material attribute. However, the application did not include solubility information for (b) (4).

Reviewer's Note:

On 4/3/2017, an IR was sent to the Applicant requesting to provide (b) (4), and to submit the aqueous solubility data for (b) (4) over the physiologic pH range. Additionally, in order to understand the effects of (b) (4) on drug solubilization, the Applicant was also requested to provide aqueous solubility data of (b) (4) over the physiologic pH range (refer to Appendix 1).

On 4/28/2017, the Applicant responded to the above 4/3/2017 IR. The Applicant evaluated and compared various lots of (b) (4). The provided data showed that the solubility of spironolactone was independent of pH (Appendix 1, Table 1). Moreover, the thermodynamic solubility of the (b) (4) did not differ significantly. (b) (4) exhibited similar dissolution over the studied physiologic pH range.

Permeability

No permeability data for spironolactone from the proposed drug product was provided by the Applicant.

4. DISSOLUTION INFORMATION

The Applicant studied the dissolution of the proposed product, Carospir™ (Spironolactone), suspension, 25 mg/5 mL, in various dissolution media (b) (4)

The drug dissolution data generated in media with various pH conditions indicate that the proposed drug product is poorly soluble and hence exhibits incomplete dissolution.

Dissolution Method and Acceptance Criterion

The proposed dissolution method and acceptance criterion are summarized in Table 2.

Table 2. Dissolution method and acceptance criterion initially proposed by the Applicant

Apparatus	USP Apparatus 2 (paddle)
Paddle Speed	25 rpm
Volume	900 ml
Medium	0.1N HCl containing (b) (4) % Cetrimonium Bromide
Temperature	37.0 ± 0.5°C
Acceptance Criterion	Not less than (b) (4) % (Q) at (b) (4) minutes

Evaluation of (b) (4) for Spironolactone Tablets

(b) (4)

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(b) (4)

Dissolution Acceptance Criterion

The Applicant proposed dissolution acceptance criterion of 'Not less than (NLT) (b) (4) % (Q) of the drug release in (b) (4) minutes'. In the 'Justification for Specifications of the Drug Product' section (Module 3.2.P.5.6) the Applicant stated that the proposed dissolution acceptance criterion is based on the comments provided by the FDA via a written response for a type-B meeting for the IND 120929 (Dated 02/11/2014).

➤ **REVIEWER'S ASSESSMENT FOR DISSOLUTION METHOD DEVELOPMENT**

(b) (4)

(b) (4)

(b) (4)

The data indicate that 0.01% CTAB is an appropriate concentration for the proposed dissolution method. However, the Applicant requested to keep the originally proposed dissolution method. To justify their proposal, the Applicant argued that the original dissolution method was sensitive and discriminating towards changes in the drug particle size in the suspension.

To show the discriminating power of the proposed method, the Applicant prepared two batches of the drug product, one with (b) (4) and the other one with (b) (4). The particle size of (b) (4) used in manufacture of batch D1401-136 was (b) (4) μm , (b) (4) μm , and (b) (4) μm for the D (v,0.1), D (v,0.5) and D (v,0.9), respectively. The particle size of the (b) (4) was (b) (4) μm , (b) (4) μm , and (b) (4) μm , for the D (v,0.1), D (v,0.5) and D (v,0.9) respectively. CMP has committed to (b) (4) for the manufacture of the proposed drug product, and the release specifications of the API include a particle size specification. The dissolution data of the batches with (b) (4) generated using the proposed dissolution method is summarized in Table 8.

Table 8: Dissolution profiles of drug products prepared with (b) (4)

Time (Minutes)	Batch D1401-136 (b) (4)		Batch D1401-96 (b) (4)	
	Mean	%RSD	Mean	%RSD
5	50	0.8	91	1.3
10	66	0.0	98	0.5
15	73	0.7	99	0.4
30	81	0.0	100	0.5
45	83	0.5	99	0.5
60	84	0.5	99	0.4

The provided data show that the dissolution profiles of the two batches are different (similarity factor $f_2 = 28.8$). The data show that the proposed dissolution method is sensitive towards change in drug particle size in the proposed product. For a suspension, drug particle size is one of the most critical material attributes and hence, the selection of the proposed dissolution method is justified. However, in general, FDA recommends that the (b) (4)

(b) (4)

➤ **REVIEWER'S ASSESSMENT FOR PROPOSED ACCEPTANCE CRITERION**

The Applicant proposed dissolution acceptance criterion of 'Not less than (NLT) (b) (4) % (Q) of the drug release in (b) (4) minutes' is (b) (4) and the provided dissolution data fully support the setting of a (b) (4) acceptance limit. On the basis of dissolution data for the dissolution method with 0.01% CTAB summarized in Table 8, a dissolution acceptance criterion of 'Not less than (b) (4) % (Q) at 15 minutes' is recommended for the proposed drug product.

On 5/15/2017, the Applicant was requested to implement the following dissolution method and acceptance criterion for the proposed drug product for release and on stability (see Appendix 2).

Recommended Dissolution Method and Acceptance Criterion for Carospir™ (Spironolactone), Oral suspension	
Apparatus	USP Apparatus 2 (paddle)
Paddle Speed	25 rpm
Volume	900 ml
Medium	0.1N HCl containing 0.01% Cetrimonium Bromide
Temperature	37.0 ± 0.5 C
Acceptance Criterion	Not less than (b) (4) % (Q) at 15 minutes

On 5/26/2017, the Applicant agreed to the change in dissolution medium and (b) (4) dissolution acceptance criterion for their drug product.

5. BRIDGING STUDIES

There were no in-vitro and/or in-vivo bridging studies needed because of the following:

- There were no changes in the composition of the proposed product between the clinical batch, exhibit batches, and the proposed commercial batches; with the exception of a minor change in the quantities of (b) (4)
- There was no change in the manufacturing site for the proposed product. Clinical and exhibit batches were manufactured at the same site as the proposed site for the commercial batches. While the batch size for the exhibit lots was (b) (4) Kg, the batch size for the commercial lots is proposed to be (b) (4) Kg.
- There were no major changes in the manufacturing process in the scale-up.

6. CONCLUSIONS AND RECOMMENDATION

The Applicant's overall development and validation of the dissolution method are adequate. The dissolution method (*USP Apparatus 2 @ 25 rpm; 900 ml 0.1N HCl with 0.01% Cetrimonium Bromide at 37°C*) and acceptance criterion of Q = (b) (4) % at 15 minutes are acceptable for the quality control of Carospir™ (Spironolactone), oral suspension, 25 mg/5 mL at release and on stability.

From the Biopharmaceutics perspective, NDA 209478 for Z Carospir™ (Spironolactone), oral suspension, 25 mg/5 mL, is recommended for **APPROVAL**.

Appendix 1

Biopharmaceutics Information Request Comments sent to the Applicant on 04/03/2017, and the Applicant's responses received on 04/28/2017

1. *We are aware that there are three polymorphs for Spironolactone.* (b) (4)

Applicant's Response

(b) (4)

(b) (4) The results are given as an average of two parallel measurements. See Table 2 for results. The results show that the solubility of Spironolactone is independent of pH. Moreover, the thermodynamic solubility of (b) (4) does not differ significantly. While (b) (4) exhibit similar dissolution, the solubility of (b) (4) is slightly greater than that of (b) (4)

Table 1: Solubility of Spironolactone in aqueous media (µg/mL)

Solvent	(b) (4)			
	Lot # R720042	Lot # R72110N	Lot # 271101N	Lot # J71085N
pH 1	31	28	31	27
pH 4.5	32	25	26	25
pH 6.8	32	25	23	24
pH 7.4	32	30	26	26

2. Please provide aqueous solubility data of the (b) (4) over the physiologic pH range.

Applicant's Response

Please see response to Question 1 above.

3. The provided dissolution data suggest that cetrimonium bromide (CTAB) concentration in the proposed dissolution medium (b) (4). Therefore, provide additional dissolution profile data with (b) (4). We recommend that the (b) (4).

Applicant's Response

Please see [Predictive Dissolution Method](#) for a summary of the development activities performed to support the proposed dissolution method (b) (4) including particle size discrimination ability. The dissolution method developed using (b) (4), is a suitable Quality Control procedure. CMP has committed to (b) (4) for the manufacture of this drug product, the release specifications of the API include a particle size specification and we have shown that the proposed dissolution method can discriminate between particle size differences. These controls along with the addition of a release and stability specification for particle size in the drug product (See [Question and Response # 3](#)) would provide appropriate means of controlling and monitoring this critical manufacturing variable. We do not feel that (b) (4) would provide any additional benefit. In the STUDY MAY PROCEED correspondence for IND 120929 dated 11/23/2015, the communication indicated that the dissolution method proposed in the dissolution method development report “appears appropriate” and therefore the release and stability data were generated using the proposed dissolution procedure.

However, as requested, CMP evaluated (b) (4). As expected, the (b) (4).

(b) (4)

(b) (4)

4. *Provide data supporting the discriminating ability of the proposed dissolution method for the most relevant critical manufacturing variables, such as particle size, as per the advice comments provided in our written response dated February 11, 2014 under IND 120929.*

Response

Please see [Predictive Dissolution Method](#) (Section VI) for a summary and discussion of the development activities performed to support the proposed dissolution method ((b) (4) % CTAB), including particle size discrimination ability.

Appendix 2

Biopharmaceutics Information Request Comments sent to the Applicant on 05/15/2017, and the Applicant's responses received on 05/26/2017

1. Based on the provided dissolution data, we consider that 0.01% is the appropriate amount of Cetrimonium Bromide surfactant needed for the dissolution test of your drug product. Also, the data fully support the setting of a (b) (4) acceptance criterion. Therefore, please implement the following dissolution method and acceptance criterion for batch release and stability testing of your proposed drug product:

<i>Recommended Dissolution Method and Acceptance Criterion for Carospir™ (Spironolactone), Oral suspension</i>	
<i>Apparatus</i>	<i>USP Apparatus 2 (paddle)</i>
<i>Paddle Speed</i>	<i>25 rpm</i>
<i>Volume</i>	<i>900 ml</i>
<i>Medium</i>	<i>0.1N HCl containing 0.01% Cetrimonium Bromide</i>
<i>Temperature</i>	<i>37.0 ± 0.5°C</i>
<i>Acceptance Criterion</i>	<i>Not less than (b) (4) % (Q) at 15 minutes</i>

Applicant's Response

CMP Pharma agrees to the change in dissolution medium and (b) (4) dissolution acceptance criterion as proposed by the Agency. Please refer to Section 3.2.P.5.1 for the revised drug product specifications and Section 3.2.P.5.2 for the drug product Analytical Procedure. Aspects of method validation were performed for the revised dissolution method. Please refer Section 3.2.P.5.3 for the updated method validation report and protocol.

2. Please revise as appropriate the corresponding sections of your NDA submission and provide a copy of the specifications for the drug product with the revised dissolution test (method and acceptance criterion).

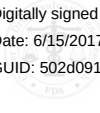
Applicant's Response

Please refer Sections 3.2.P.5.1, 3.2.P.5.2 and 3.2.P.5.3 for updated drug product specifications and drug product test method.



Angelica
Dorantes

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Product Quality Microbiology Review

8 May 2017

NDA: 209478

Drug Product Name

Proprietary: Carospir

Non-proprietary: Spironolactone oral suspension, 25 mg/5 mL

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
10/3/2016	10/4/1016		11/1/2016
4/28/2017	4/28/17		

Applicant/Sponsor

Name: CMP Pharma, Inc.

Address: P.O. Box 147, 8026 US Highway 264A, Farmville, NC, 27828

Representative: Ellen Barkley, Regulatory Specialist

Telephone: 252-753-7111

Name of Reviewer: Jason M. God, Ph.D.

Conclusion: Recommended for approval

Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** Original NDA
 2. **SUBMISSION PROVIDES FOR:** Initial marketing of a non-sterile, aqueous, oral suspension
 3. **MANUFACTURING SITE:** CMP Pharma
8026 US Highway 264A
Farmville, NC 27828
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** (b) (4) non-sterile, aqueous liquid; oral; 25 mg/5 mL
 5. **METHOD(S) OF STERILIZATION:** N/A
 6. **PHARMACOLOGICAL CATEGORY:** (b) (4)
(b) (4)
(b) (4)
(b) (4)
- B. **SUPPORTING/RELATED DOCUMENTS:** (NONE)
- C. **REMARKS:** An information request was sent by the Agency to the applicant, dated 3 April 2017. Responses from the applicant were received 28 April 2017. The review of the applicant's response has been incorporated into the appropriate sections of the review.

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Executive Summary**I. Recommendations**

- A. Recommendation on Approvability** – Recommended for approval
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – (None)

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – None. Drug product is non-sterile.
- B. Brief Description of Microbiology Deficiencies** – Based on the information submitted in the application, no Microbiology deficiencies were identified.
- C. Contains Potential Precedent Decision(s)-** ☐ Yes ☒ No
(If yes, provide a brief description and a reference to the page where the precedent is discussed in depth)

IV. Administrative

- A. Reviewer's Signature** _____
Jason M. God, Ph.D.
- B. Endorsement Block**
Neal J. Sweeney, Ph.D., Microbiology Quality Assessment
Lead (Acting)
- C. CC Block**
N/A

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- Description of drug product – White to off-white, opaque suspension, with banana odor/flavor.
- Drug product composition –

Table 1: Qualitative and quantitative composition of Carospir

Ingredient	Quality Standard	Function	% w/v	Quantity/mL (mg/mL)	Quantity/mL (mg/5 mL)
Spirolactone, (b) (4)	USP	API	0.5000	5.000	25.00
Xanthan Gum	NF	(b) (4)			
Simethicone Emulsion (b) (4)	USP				
Sorbic Acid	NF				
Potassium Sorbate	NF				
Sodium Saccharin	USP				
Citric Acid Anhydrous ¹	USP				
Sodium Citrate Dihydrate ¹	USP				
Magnasweet 110	In-house				
Glycerin	USP				
Banana Flavor (b) (4) ²	In-house				
Purified Water	USP				

Table 1 was reproduced from the Applicant's Table 2, 3.2.P.1

- Description of container closure system – 4 oz or 16 oz amber (b) (4) bottles with white (b) (4) caps.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

(b) (4)

P.3.1 Manufacturers

CMP Pharma, Inc.
8026 US Highway 264A
Farmville, NC 27828

P.3.3 Description of the Manufacturing Process and Process Controls

The drug product is

(b) (4)

ADEQUATE

REVIEWER COMMENT – Description of drug product and pharmaceutical development information were consistent with the FDA Guidances for Industry: (1) Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products, and (2) Q8(R2) Pharmaceutical Development.

P.5 Control of Drug Product**P.5.1 Specifications**

Release and stability specifications are as follows:

- Total aerobic microbial count: $\leq$ (b) (4) cfu/mL
- Total combined yeast and molds count: $\leq$ (b) (4) cfu/mL
- Absence of: *Escherichia coli* and *Bulkholderia cepacia*

The stated specifications conform to USP <1111>, aqueous preparations for oral use.

P.5.2 Analytical Procedures

- Microbial limits – Tested per USP <61> for Total Aerobic Microbial Count and Total Combined Yeast and Mold count. Method suitability was performed per USP <61> and supports routine testing for TAMC and TYMC. USP <62> testing performed for absence of *E. coli* and *B. cepacia*.

ADEQUATE

REVIEWER COMMENT – The applicant has demonstrated the suitability of USP <61> for routine testing of the drug product. Testing for *B. cepacia* has been included in USP <62> testing, satisfying the Agency's requirement for testing of *B. cepacia* in non-sterile, aqueous preparations.

P.8 Stability**P.8.1 Stability Summary and Conclusion**

The proposed shelf life is 18 months for the 4 oz presentation and 24 months for the 16 oz presentation, stored at 20-25°C. In-use shelf life of the drug product is 30 days.

For both presentations (4 oz and 16 oz) stability studies are ongoing for drug product stored upright and horizontally under long-term ($25\pm 2^{\circ}\text{C}/40\pm 5\%\text{RH}$), intermediate ($30\pm 2^{\circ}\text{C}/65\pm 5\%\text{RH}$) and accelerated ($40\pm 2^{\circ}\text{C}/25\%\text{RH}$) conditions. Microbial limits (b) (4) testing are performed at 0 and 6 months for accelerated samples, 0, 12, 18 and 24 months for long-term samples and 0 and 12 months for intermediate samples.

P.8.2 Post-Approval Stability Protocol and Stability Commitment

The applicant commits to performing long-term stability on the first three commercial batches of drug product. Annually, thereafter, one batch will be placed on long-term stability.

- Microbial Limits – (b) (4) microbial limits will be tested at 0, 12, 18 and 24 months for the 4 oz presentation and 0, 12, 18, 24, 30 and 36 months for the 16 oz presentation.

P.8.3 Stability Data

Stability data is provided through 12 months of testing and all results are acceptable for (b) (4) microbial limits and absence of *E. coli* and *B cepacia*. Data provided for 1 month in-use stability (to simulate typical in-use conditions) are also acceptable for (b) (4) microbial limits and absence of *E. coli* and *B cepacia*.

ADEQUATE

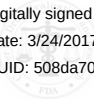
REVIEWER COMMENT –

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS: (None)



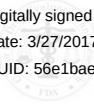
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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment – NDA 209478 Spironolactone Oral Suspension 25 mg/5 mL (5 mg/mL)

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Assay – Active	Raw materials Formulation Container closure Process/Scale/Equipment/Site	Moderate	In-process and end product testing at release and on stability;	Acceptable	
Assay - (b) (4)	Raw materials Formulation Container closure Process/Scale/Equipment/Site	Low	End product testing at release and on stability; (b) (4) established during development	Acceptable	(b) (4)
Phase Separation	Raw materials Formulation Process/Scale/Equipment/Site	Low	Aqueous formulation; All excipients have sufficient aqueous solubility; Drug substance insoluble in water; Formulated as a suspension (b) (4)	Acceptable	

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
(b) (4)	Raw materials Formulation Process/Scale/Equipment/Site	Low	(b) (4)	Acceptable	Changes to drug substance supplier, formulation components, manufacturing process, container closure should be evaluated for potential (b) (4)
Degradants/Related Substances	Raw materials Formulation Container closure Process/Scale/Equipment/Site	Low	End product testing at release and on stability; Major degradant is active metabolite	Acceptable	
(b) (4)	Raw materials Formulation Process/Scale/Equipment/Site	Moderate	(b) (4)	Acceptable	
Dosing accuracy	Raw materials Formulation Container closure Process/Scale/Equipment/Site	Low	End product testing for viscosity and delivered volume at release and on stability serve as surrogate measures of dosing accuracy; (b) (4)	Acceptable	Weight loss caused by water evaporation from the semi-permeable bottle may result increases in viscosity which can impact dosing accuracy

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Palatability	Raw materials Formulation Process/Scale/Equipment/Site	Moderate	Formulated with flavor (b) (4)	Acceptable	
Microbiological quality	Raw materials Formulation Container closure Process/Scale/Equipment/Site	Low	End product testing at release and on stability: (b) (4) container closure suitable to ensure microbiological quality	Acceptable	
Leachables	Raw materials Formulation Container closure Process/Scale/Equipment/Site	Moderate	Moderate formulation pH does not elevate risk for leachables; Leachables characterized for product/container closure and demonstrated that extracted substance content was very low and migrating substances were not detected	Acceptable	
Dissolution	Raw materials Formulation Process/Scale/Equipment/Site	Low	End product testing at release and on stability; Commercial dissolution method considered discriminatory	Acceptable	
pH	Raw materials Formulation Container closure Process/Scale/Equipment/Site	Low	(b) (4) end product testing at release and on stability	Acceptable	
Viscosity	Raw materials Formulation Container closure Process/Scale/Equipment/Site	Moderate	(b) (4) end product testing at release and on stability	Acceptable	Weight loss caused by water evaporation from the semi-permeable bottle may result increases in viscosity

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Content uniformity	Raw materials Formulation Container closure Process/Scale/Equipment/Site	Moderate	(b) (4) end product testing at release and on stability	Acceptable	
Resuspendability	Raw materials Formulation Container closure Process/Scale/Equipment/Site	Moderate	Labeling instructions include direction to shake well before using; (b) (4) along with end product testing for viscosity and uniformity are surrogate measures; Development data demonstrate that shaking for between 5 and 15 seconds results in uniform samples for fresh and aged product	Acceptable	Weight loss caused by water evaporation from the semi-permeable bottle may result increases in viscosity and lead to issues with ability to adequately shake to resuspend
Particle Size	Raw materials Formulation Process/Scale/Equipment/Site	Low	End product testing added to control strategy at release and on stability	Acceptable	No trends in particle size were observed in stability but should be monitored as more data is collected to confirm
Weight Loss	Raw materials Formulation Container closure Process/Scale/Equipment/Site	Moderate	End product testing added to control strategy at release and on stability	Acceptable	Weight loss from container closure observed in stability data



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