CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209478Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Section 1.3.5.2: Patent Certifications

Statement of No Relevant Patents

for

NDA No. 209478

Spironolactone Oral Suspension, 25 mg/5mL

Pursuant to section 21 C.F.R. § 314.94(a)(12)(ii), CMP Pharma, Inc. hereby certifies that in our opinion and to the best knowledge of CMP Pharma Inc., there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

Sincerely,

September 28, 2016

Gerald Sakowski
CEO
CMP Pharma, Inc.

EXCLUSIVITY SUMMARY

NDA # 209478 SUPPL # HFD #

Trade Name CaroSpir

Generic Name Spironolactone Oral Suspension, 25 mg/5 mL

Applicant Name CMP Pharma, Inc.

Approval Date, If Known August 4, 2017

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The applicant conducted two relative bioavailability studies, comparing spironolactone oral suspension to the listed drug (LD) Aldactone® (NDA 12,151). One of these studies was conducted comparing a 25 mg Aldactone® tablet to spironolactone oral suspension, and another comparing 100 mg tablets to spironolactone oral suspension. In addition, a food-effect study was conducted on spironolactone oral suspension at 100 mg. The results show that the bioavailability of spironolactone suspension is 15% and 37% higher than the LD at 25 mg and 100 mg tablet strengths, respectively. To address the higher exposures, of the Agency proposed a dose adjustment between 25 mg and 100 mg, to

which the applicant agreed.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including

salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# NDA 12151 Aldactone oral tablets

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☒

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to

disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Brian Proctor
Title: Regulatory Project Manager
Date: 8/3/2017

Name of Division Director signing form: Norman Stockbridge, M.D., Ph.D.
Title:

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BRIAN L PROCTOR
08/03/2017

NORMAN L STOCKBRIDGE
08/03/2017

Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

BACKGROUND

Please check all that apply: ☐ **Full Waiver** ☒ **Partial Waiver** ☐ **Pediatric Assessment** ☒ **Deferral/Pediatric Plan**

BLA/NDA#: NDA 209478

PRODUCT PROPRIETARY NAME: CaroSpir®

ESTABLISHED/GENERIC NAME: Spironolactone Oral Suspension, 25 mg/5 mL) Oral Suspension

APPLICANT/SPONSOR: CMP Pharma, Inc

PREVIOUSLY APPROVED INDICATION/S: None.

PROPOSED INDICATION/S (these indications match those of the reference listed drug):

(b) (4)

[redacted]

BLA/NDA STAMP DATE: 10/4/2016

PDUFA GOAL DATE: 8/4/2017

Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

NEW ☐ ***active ingredient(s) (includes new combination);*** ☐ ***indication(s);*** ☒ ***dosage form;*** ☐ ***dosing regimen; or*** ☐ ***route of administration?***

Did the sponsor submit an Agreed iPSP? Yes ☒ ***No*** ☐

Are there any changes to the Agreed iPSP that are different than the sponsor's current pediatric plan? Yes ☒ ***No*** ☐

The Agreed Initial Pediatric Study Plan described two studies:

- (b) (4) pharmacokinetics study" of Spironolactone Oral Suspension in pediatric patients with edematous condition. In this study, (b) (4) patients 0 to <17 years of age would be treated with spironolactone oral suspension (b) (4) Stated primary objectives of this study include: determination of pharmacokinetic (PK) parameters in pediatric patients (b) (4) .
- (b) (4) safety study of Spironolactone Oral Suspension in pediatric patients with edematous conditions. (b) (4) pediatric patients 0 to < 17 years of age would be enrolled in this study (b) (4) The primary endpoint in this study would be (b) (4)

In lieu of the proposed studies, the Division recommended that the sponsor conduct the two studies described below (see advice letter dated March 23, 2017).

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)

Yes ☐ ***No*** ☒

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes ☐ ***No*** ☒

If Yes, PMR #_____ NDA #_____

Does the division agree that this is a complete response to the PMR? Yes ☐ ***No*** ☐

If Yes, to either question Please complete the Pediatric Assessment Template.

If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group

WAIVER REQUEST

Please attach:

☐ ***Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.***

☐ ***Pediatric Record***

1. Pediatric age group(s) to be waived.

(b) (4) indications are to be waived for the following reasons:

- Hypertension indication is waived because treatment requires chronic administration of the drug product for adequate control. The antiandrogenic, progestogenic and estrogenic activities of spironolactone present significant safety concerns. This evidence strongly suggests that spironolactone would be unsafe in all pediatric age groups for this chronic use.

(b) (4)

- The heart failure indication is waived because the causes and mechanisms of heart failure are different in children and adults. Heart failure in children is most commonly caused by congenital heart malformations and cardiomyopathy whereas the primary etiology of adult heart failure is ischemic heart disease due to atherosclerotic coronary artery disease. The form of heart failure seen in adults is rare in children; hence conducting a trial is highly impractical.

2. Reason(s) for waiving pediatric assessment requirements (***Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for <u>each</u> age group or indication. This section should reflect the Division's thinking.***)

☒ Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from the adult-related conditions on the next page. (Heart Failure Indication)

☒ The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information MUST be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail. (Hypertension (b) (4) Indications)

☐ The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

☐ Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted. ***(This reason is for Partial Waivers Only)***

3. *Provide justification for Waiver:* See above.

4. *Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language:*

(b) (4)

Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics

These conditions qualify for waiver because studies would be impossible or highly impractical.

actinic keratosis
acute bacterial exacerbations of chronic bronchitis (a complication of chronic obstructive pulmonary disease)
adjunctive treatment of major depressive disorder
age-related macular degeneration
Alzheimer's disease
amyloidosis
amyotrophic lateral sclerosis
androgenic alopecia
ankylosing spondylitis
atherosclerotic cardiovascular disease
benign monoclonal gammopathy
benign prostatic hyperplasia
cancer:
- basal cell and squamous cell skin cancer
- bladder
- breast
- cervical
- colorectal
- cholangiocarcinoma
- endometrial
- esophageal
- follicular lymphoma
- gastric
- hairy cell leukemia
- hepatocellular
- indolent non-Hodgkin lymphoma
- liposarcoma
- lung (small & non-small cell)
- multiple myeloma
- oropharynx (squamous cell)
- ovarian (non-germ cell)
- pancreatic
- prostate
- refractory advanced melanoma
- renal cell
- uterine
- chronic lymphocytic leukemia

chronic obstructive pulmonary disease
cryoglobulinemia
diabetic peripheral neuropathy/macular edema
diabetic foot infections
digestive disorders (gallstones)
dry eye syndrome (keratoconjunctivitis sicca)
dupuytren's disease and manifestations
erectile dysfunction essential thrombocytosis
giant cell arteritis
gout
Huntington's chorea
idiopathic pulmonary fibrosis
infertility & reproductive technology
juvenile psoriatic arthritis
memory loss
menopause and perimenopausal disorders
mesothelioma
microscopic polyangiitis
myelodysplasia
myelofibrosis & myeloproliferative disorders
opioid induced constipation in chronic, non-cancer pain
osteoarthritis
overactive bladder
Parkinson's disease
paroxysmal nocturnal hemoglobinuria
plasma cells and antibody production disorders
polycythemia vera
polymyalgia rheumatica (PMR)
postmenopausal osteoporosis
prevention of stroke and systemic embolic events in atrial fibrillation
psoriatic arthritis
reduction of thrombotic cardiovascular events in patients with coronary artery disease
replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone
retinal vein occlusions
stress urinary incontinence
temporary improvement in the appearance of caudal lines
treatment of incompetent great saphenous veins and varicosities
treatment of Hypoactive Sexual Desire Disorder (HSDD) in postmenopausal women
type 2 diabetic nephropathy
vascular dementia/vascular cognitive disorder/impairment

DEFERRAL REQUEST

Please attach:

☐ ***Pediatric Record***

1. **Age groups included in the deferral request: 0 to < 17 years**

2. **Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request:**

3. **Reason/s for requesting deferral of pediatric studies in pediatric patients with disease:** (***Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for <u>each</u> age group or indication. This section should reflect the Division's thinking.***)

   Adult studies are completed and ready for approval

4. **Provide projected date for the submission of the pediatric assessment (deferral date):**

   January 2027

5. **Did applicant provide certification of grounds for deferring assessments?** ☒ **Yes** ☐ **No**

6. **Did applicant provide evidence that studies will be done with due diligence and at the earliest possible time?** ☐ **Yes** ☐ **No**

   We would like to discuss the proposed timelines for protocol submission with the PeRC.

SPONSOR'S PROPOSED PEDIATRIC PLAN

1. **Has a pediatric plan been submitted to the Agency?** ☒ **Yes** ☐ **No**

2. Does the division agree with the sponsor's plan? ☐ **Yes** ☒ **No**

As previously noted, the division recommended that CMP Pharma conduct the studies described below in lieu of the studies described in the Agreed iPSP. In email correspondence received June 28th, the applicant stated that CMP Pharma "…commits to incorporating this advice into the design of the Pediatric Study Plans."

3. **Did the sponsor submit a timeline for the completion of studies (must include at least dates for protocol submission, study completion and studies submitted)?** ☒ **Yes** ☐ **No**

Single Dose PK study in pediatric patients with edematous conditions [redacted] (b) (4)

Estimated protocol submission date:	August 2018
Estimated study initiation date:	August 2019
Estimated study completion date:	August 2020
Estimated final report submission date:	January 2021

Efficacy and safety study in pediatric patients with edematous conditions [redacted] (b) (4)

Estimated protocol submission date:	January 2022
Estimated study initiation date:	January 2023
Estimated study completion date:	January 2026
Estimated final report submission date:	January 2027

4. **Has a Written Request been issued? ☐ Yes ☒ No (If yes and the WR matches the proposed pediatric plan, please attach a copy. It is not necessary to complete the remainder of this document)**

5. **Has a PPSR been submitted? ☐ Yes ☒ No (If yes, you may submit a draft WR and have PeRC review WR and deferral/plan at the same time.)**

Please note that the remainder of this section should be completed based on what the Division is requiring regardless of what the sponsor is proposing.

DIVISION'S PROPOSED PK, SAFTEY, AND EFFICACY TRIAL

Nonclinical Studies:
The excipients are acceptable from a CMC/pharm-tox perspective. Juvenile nonclinical toxicology studies have not been performed and are not felt to be needed given the extensive clinical experience in children in which endocrine-related effects have been reported, including gynecomastia, mastalgia, anti-testosterone effects, impotence, and menstrual irregularities.

Clinical Studies:
Study 1: Single-dose PK study in the target population to characterize PK characteristics. The objective of this study should be to determine the relevant PK parameters of Spironolactone Oral Suspension in pediatric patients with edema (target population). The results of this study should be used to derive the doses that will be evaluated in Study 2. The dose or doses that will be evaluated in each age subgroup should be based on the

available adult and pediatric data on doses needed to achieve efficacy (treat edema) in this population. Dosing should commence in adolescent patients; consecutively younger age groups may be enrolled once information from the prior age group becomes available.

Study 2: Multiple-dose PK-PD study in patients with edematous conditions. The objectives of this study are (1) to determine the exposure-response relationship for Spironolactone Oral Solution in the target population following multiple doses and (2) to identify a safe and effective treatment regimen.

(b) (4)

As an alternative to conducting two separate studies as described above, it may be possible to conduct a single two-part study that incorporates the design features noted above.

Age group and population (indication) in which study will be performed:
Population for both studies: Pediatric patients with edematous conditions (b) (4) .

Age range for both studies: Patients age 0 to < 17.

Number of patients to be studied or power of study to be achieved:

Study 1: The study should be adequately powered to characterize key PK variables.

Study 2: The study should be adequately powered to assess common adverse events and effects on PD/efficacy endpoints.

Entry criteria:

Key Inclusion Criterion: Edema (b) (4)
Key Exclusion Criteria: (b) (4).

Clinical endpoints:

Study 1: PK parameters of interest such as C_{max}, T_{max}, apparent CL and V_d, $T_{1/2}$, AUC, k_{el}

Study 2: PD/efficacy endpoints of interest (b) (4)

Timing of assessments

(b) (4)

Statistical information (statistical analyses of the data to be performed): Descriptive statistics.

Division comments on product safety:
Are there any safety concerns currently being assessed? ☐ **Yes** ☒ **No**
(b) (4)

Are there safety concerns that require us to review post-marketing safety data before fully designing the pediatric studies? ☐ **Yes** ☒ **No**

Will a DSMB be required? ☒ **Yes** ☐ **No**

Other comments: None.

Division comments on product efficacy:
This product is an oral suspension of an approved product, spironolactone, approved in 1960.

Division comments on sponsor proposal to satisfy PREA:
As previously indicated, the Division is recommending that the sponsor conduct the aforementioned studies in lieu of the studies proposed in the Agreed iPSP. In email correspondence received June 28th, the applicant stated that CMP Pharma "…commits to incorporating this advice into the design of the Pediatric Study Plans.

Other comments/recommendations that were sent to CMP Pharma (see the Division's Advice Letter dated March 23, 2017):

- Information on the pathways involved in spironolactone metabolism is not currently available, but may be useful to assess the need for dose adjustment in different age groups. Therefore, we ask that you assess whether spironolactone is a substrate or an inhibitor/inducer for drug metabolizing enzymes in vitro.

- Consideration should be given to adding an open-label extension phase to Study 2 in which doses are titrated as needed to control edema. Including such a phase will provide insight into safety, including effects on potassium, at doses needed to adequately manage edema.

- We encourage you to work with experts in the disease area in designing these studies to ensure that study protocols are feasible and acceptable to investigators, parents and patients.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BRIAN L PROCTOR
08/03/2017

PHARMA

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

INTL +1.252.753.7111
USA 800.227.6637
FAX 252.753.3882

info@cmppharma.com
cmppharma.com

DEBARMENT AND CONVICTIONS CERTIFICATION

Pursuant to Section 306(k) of the Federal Food, Drug and Cosmetic Act, as amended by the Generic Drug Enforcement Act of 1992, CMP Pharma, Inc. (Address: 8026 Highway 264A, Farmville, NC 27828) certifies that CMP Pharma, Inc. has not used, and will not use in any capacity, the services of any person or firm debarred under sections 306(a) or (b) in connection with this application.

CMP Pharma, Inc. also certifies that within the previous 5 years, there have been no convictions that is described in subsections 306(a) or (b) of the Generic Drug Enforcement Act. In addition, no person or other affiliated persons responsible for the development or submission of this application has been convicted of an offense described in the subsections 306(a) or (b) of the Generic Drug Enforcement Act of 1992.

Sincerely,

CMP Pharma, Inc.

Gerald Sakowski
CEO

Date: 6/15/16

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 209478 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: CaroSpir® Established/Proper Name: Spironolactone Dosage Form: Oral Suspension		Applicant: CMP Pharma Inc. Agent for Applicant (if applicable):
RPM: Brian Proctor		Division: Cardiovascular and Renal Products

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☒ No changes
☒ New patent/exclusivity *(notify CDER OND IO)*
Date of check: 8/3/2017

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is August 4, 2017	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval, August 4, 2017
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	December 15, 2016 December 12, 2016
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ None DMEPA: December 30, 2016 DMPP/PLT (DRISK): ☒ None OPDP: July 25, 2017 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: Nonclinical May 4, 2017
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	November 30, 2016 August 1, 2017
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☐ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC July 19, 2017 If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ No mtg
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	March 7, 2017
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☒ None
Cross-Discipline Team Leader Review *(indicate date for each review)*	August 3, 2017
PMR/PMC Development Templates *(indicate total number)*	(3) August 3, 2017
Clinical	

❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	July 28, 2017
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Financial Disclosure located in the Clinical Pharmacology review addendum.
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	July 7, 2017
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	June 5, 2017
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	June 13, 2017

[5] For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Nonclinical ☒ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☐ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☐ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	June 29, 2017
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	Biopharm June 15, 2017
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	June 29, 2017
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	June 30, 2017 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☒ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	
❖ Take Action Package (if in paper) down to Document Room for scanning within **two business days**	

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BRIAN L PROCTOR
08/17/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209478

GENERAL ADVICE

CMP Pharma, Inc.
Attention: Gerald Sakowski
Chief Executive Officer
PO Box 147
8026 US Highway 264A
Farmville, NC 27828

Dear Mr. Sakowski:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Spironolactone Oral Suspension, 25 mg/ 5 mL.

We also refer to your June 14, 2017 submission, containing a response to the Division's May 8, 2017 General Advice Letter.

We have reviewed the referenced material and have the following comment:

We do not agree with your proposal to (b) (4)

If you have any questions, please call Brian Proctor, Regulatory Project Manager, at (240) 402-3596.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NORMAN L STOCKBRIDGE
06/19/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209478

General Advice

CMP Pharma, Inc.
Attention: Gerald Sakowski
Chief Executive Officer
PO Box 147
8026 US Highway 264A
Farmville, NC 27828

Dear Mr. Sakowski:

Please refer to your New Drug Application (NDA) dated October 3, 2016, received October 4, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Spironolactone Oral Suspension, 25 mg/ 5 mL.

During review of your submission we have identified the following issues, which have implications for labeling.

1. The bioavailability of the spironolactone suspension is approximately 15% higher compared to spironolactone 25-mg tablets and 35% higher compared to spironolactone 100-mg tablets, and the excursions for C_{max} are even larger. This suggests that a dose reduction may be needed when transitioning patients from stable therapy with the tablet formulation to your product. It also raises the question of whether labeling should recommend a lower starting dose of your product as compared to the recommended staring dose of the reference listed drug (RLD). We acknowledge that there is no labelled dose reduction for the RLD for an increase in exposure of almost 100% with food. Nevertheless, we are concerned about the potential combined effect of an increase in exposure due to food and the higher bioavailability with the suspension.
2. The label for the RLD does not contain information on the dose proportionality of spironolactone tablets, and data reported in the published literature do not unequivocally resolve this issue. Since relative bioavailability estimates of your product differ when comparing your product against tablet strengths of 25 mg and 100 mg, extrapolation of relative bioavailability to doses beyond 100 mg becomes difficult. The reason for this non-proportional increase in exposure of the spironolactone suspension relative to the RLD tablets is unclear. However, it raises concern that there may be a greater difference in exposure between the suspension and tablets at doses higher than 100 mg.

In light of these issues, we have the following comments and recommendations:

- To support doses outside of the currently studied range in the pharmacokinetic studies, you should submit information delineating the dose proportionality of spironolactone with Aldactone® tablets at doses that span the clinically relevant dose range of 25 to [redacted] (b) (4) mg and the relative bioavailability of the oral suspension compared to the tablets at the respective dose levels.
- Absent the aforementioned information or a compelling rationale as to why it is not needed, we may decide to limit the approved dosing regimen of your product to between 25 mg and 100 mg daily [redacted] (b) (4).
- The dosing for oral suspension in the product insert will reflect a 25% dose reduction relative to Aldactone to adjust for the higher exposure to spironolactone from suspension between 25 mg and 100 mg. The label will need to state clearly that the product is not therapeutically equivalent to Aldactone® tablets or generics thereof.

If you have any questions, please contact Brian Proctor, Regulatory Project Manager, at (240) 402-3596.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BRIAN L PROCTOR
05/08/2017

NORMAN L STOCKBRIDGE
05/08/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209478

GENERAL ADVICE

CMP Pharma, Inc.
Attention: Gerald Sakowski
Chief Executive Officer
PO Box 147
8026 US Highway 264A
Farmville, NC 27828

Dear Mr. Sakowski:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Spironolactone Oral Suspension, 25 mg/ 5 mL.

We also refer to your September 21, 2015, submission, containing a request for deferral of pediatrics studies for the treatment of edema (b) (4) .

In your Agreed Initial Pediatric Study Plan, you proposed to conduct two studies:

- (b) (4) pharmacokinetics study" of Spironolactone Oral Suspension in pediatric patients with edematous condition. In this study, (b) (4) patients 0 to <17 years of age would be treated with spironolactone oral suspension (b) (4). Stated primary objectives of this study include: determination of pharmacokinetic (PK) parameters in pediatric patients (b) (4)
- (b) (4) safety study of Spironolactone Oral Suspension in pediatric patients with edematous conditions (b) (4) pediatric patients 0 to < 17 years of age would be enrolled in this study (b) (4). The primary endpoint in this study would be (b) (4) .

In lieu of the proposed studies, we recommend that you conduct the following studies:

Study 1: Single-dose PK study in patients with edema to characterize PK characteristics

Objective: The objective of this study should be to determine the relevant PK parameters of Spironolactone Oral Suspension in pediatric patients with edema (target population). The results of this study should be used to derive the doses that will be evaluated in Study 2.

Dosing: The dose or doses that will be evaluated in each age subgroup should be based on the available adult and pediatric data on doses needed to achieve efficacy (treat edema) in this population.

Dosing should commence in adolescent patients; consecutively younger age groups may be enrolled once information from the prior age group becomes available.

Study 2: Multiple-dose PK-PD study

Objective: The objectives of this study are (1) to determine the exposure-response relationship for Spironolactone Oral Solution in the target population following multiple doses and (2) to identify a safe and effective treatment regimen.

Please refer to the Draft Guidance for Industry – General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products, December 2014, for information on other study design considerations (e.g., sample size, number of samples per patient).

Additional Comments:

1. Information on the pathways involved in spironolactone metabolism is not currently available, but may be useful to assess the need for dose adjustment in different age groups. Therefore, we ask that you assess whether spironolactone is a substrate or an inhibitor/inducer for drug metabolizing enzymes in vitro.
2. Instead of conducting two separate studies as described above, it may be possible to conduct a single two-part study that incorporates the design features noted above.
3. Consideration should be given to adding an open-label extension phase to Study 2 in which doses are titrated as needed to control edema. Including such a phase will provide insight into safety, including effects on potassium, at doses needed to adequately manage edema.
4. We encourage you to work with experts in the disease area in designing these studies to ensure that study protocols are feasible and acceptable to investigators, parents and patients.

If you have any questions, please call Brian Proctor, Regulatory Project Manager, at (240) 402-3596.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NORMAN L STOCKBRIDGE
03/23/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209478

INFORMATION REQUEST

CMP Pharma, Inc.
Attention: Gerald Sakowski
Chief Executive Officer
PO Box 147
8026 US Highway 264A
Farmville, NC 27828

Dear Mr. Sakowski:

Please refer to your New Drug Application (NDA) dated October 3, 2016, received October 4, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Spironolactone Oral Suspension, 25 mg/ 5 mL.

We are reviewing the Clinical Pharmacology section of your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. We note that 7-alpha thiomethyl spironolactone was measured in pilot study 063-15 (as indicated on page 7 of the bioanalytical report and page 11 of the method validation report), but the results were not submitted to the NDA. Please submit the concentration vs time data as well as the pharmacokinetic parameter data for 7-alpha thiomethyl spironolactone in pilot study 063-15), including summary and individual pharmacokinetic parameter data and individual level datasets as SAS transport files (*.xpt). If the pharmacokinetic profile of 7-alpha thiomethyl spironolactone was measured in any other studies, please submit the data from these studies as well. We would like your interpretation of these data, as well.

2. Was 6-ß-hydroxy-7-α-(thiomethyl) spironolactone (HTMS) also measured in any of your studies? If so, please submit the pharmacokinetic data.

3. Submit a detailed description of the types of food used in Study 084-15, your food-effect study. In addition to filling out the following table, please also provide a list of the actual food provided, e.g. toast, butter, bacon, etc.

Fat	Protein	Carbohydrates
Absolute number of calories from fat	Absolute number of calories from protein	Absolute number of calories from carbohydrates
%of total meal calories from fat	% of total meal calories from protein	% of total meal calories from carbohydrates

4. Were any instructions provided to investigators regarding shaking or inverting of drug product or rinsing of the administration vessel for the suspension in Studies 063-15, 064-15, and 084-15? If so, please provide.

5. Submit the chromatograms for Studies 064-15 and 068-15, as recommended in Guidance for Industry - Bioanalytical Method Validation (Sep 2013).

We request a response by March 21, 2017.

If you have any questions, please contact Brian Proctor, Regulatory Project Manager, at (240) 402-3596.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NORMAN L STOCKBRIDGE
03/10/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209478

INFORMATION REQUEST

CMP Pharma, Inc.
Attention: Gerald Sakowski
Chief Executive Officer
PO Box 147
8026 US Highway 264A
Farmville, NC 27828

Dear Mr. Sakowski:

Please refer to your New Drug Application (NDA) dated October 3, 2016, received October 4, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Spironolactone Oral Suspension, 25 mg/ 5 mL.

During our preliminary review of your submitted labeling, we found that you did not provide a review and summary of the available information to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. Thus, your proposed PLLR labeling changes cannot be agreed upon until the information request is fulfilled. No partial PLLR conversions may be made.

Please resubmit the following information by February 17, 2017.

- a review and summary of all available published literature regarding spironolactone use in pregnant and lactating women,
- a revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR.

Refer to the Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

If you have any questions, please contact Brian Proctor, Regulatory Project Manager, at (240) 402-3596.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NORMAN L STOCKBRIDGE
01/24/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209478

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

CMP Pharma, Inc.
P.O. Box 147
8026 US Highway 264A
Farmville, NC 27828

ATTENTION: Ellen Barkley
Regulatory Specialist

Dear Ms. Barkley:

Please refer to your New Drug Application (NDA) dated and received October 4, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Spironolactone Oral Suspension, 25mg/5mL.

We also refer to your correspondence, dated and received October 24, 2016, requesting review of your proposed proprietary name, Carospir.

We have completed our review of the proposed proprietary name, Carospir and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your October 24, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Darrell Lyons, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4092. For any other information regarding this application, contact Brian Proctor, Regulatory Project Manager in the Office of New Drugs, at (240) 402-3596.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
12/15/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209478

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

CMP Pharma, Inc.
Attention: Gerald Sakowski
Chief Executive Officer
PO Box 147
8026 US Highway 264A
Farmville, NC 27828

Dear Mr. Sakowski:

Please refer to your New Drug Application (NDA) dated October 3, 2016, received October 4, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Spironolactone Oral Suspension, 25 mg/ 5 mL.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is August 4, 2017.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 2, 2017.

During our filing review of your application, we identified the following potential review issues:

Clinical Pharmacology

1. The results of the pivotal PK Study 064-15 indicate that CaroSpir® oral suspension and the reference listed drug (Aldactone® tablets) are not bioequivalent. Provide a

justification for bridging to the efficacy and safety of the reference listed drug that addresses these findings. Please also address the clinical relevance of the 66% increase in Cmax (relative to Aldactone®) and 37% increase in AUC (relative to Aldactone®) seen in Study 064-15 and the differences in relative bioavailability observed in Studies 063-15 and 064-15.

2. The appendices to the study reports for Studies 063-15, 064-15 and 084-15 contain a section titled "Documentation of Statistical Methods," but this section only appears to contain statistical output. Please provide the statistical analysis plans for these studies and the source code and analytical parameters for the SAS and WinNonlin analyses. If this information has already been submitted, please provide information on the specific location within the submission.

Please submit the requested information no later than January 13, 2017.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We also have the following comments and requests for information:

1. Please submit annotated labeling that identifies the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature.

2. Please submit a summary of the postmarketing safety experience for the reference listed drug and ANDA products along with a brief discussion of whether the review identified any new safety concerns in adults or children.

3. The cover letter to your IND states the following: "In accordance with section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, CMP Pharma, Inc. hereby submits this New Drug Application (NDA) for CaroSpir® (Spironolactone Oral Suspension, 25 mg/5 mL) Oral Suspension... This NDA relies on IND # 120929 originally filed on 10 Oct, 2015." We assume that application relies on the Agency's previous finding of safety and/or effectiveness for Aldactone® (NDA 012151), as stated in the submitted Form FDA 356h. Please address.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances, and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

We will review this application under the provisions of 21 CFR 314 Subpart I – *Approval of New Drugs When Human Efficacy Studies Are Not Ethical or* Unless we otherwise inform you, as required by 21 CFR 314.640, you must submit during the preapproval review period copies of all promotional materials, including promotional labeling and advertisements, intended for dissemination or publication within 120 days following marketing approval (i.e., your launch campaign). During the preapproval review period, please submit, in triplicate, a detailed cover letter (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and end each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

PREA

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We reference the deferral granted on September 21, 2016, for the pediatric study requirement for this application.

If you have any questions, please call Brian Proctor, Regulatory Project Manager, at (240) 402-3596.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NORMAN L STOCKBRIDGE
12/14/2016

Form Approved: OMB No. 0910 - 0297 Expiration Date: March 31, 2019. See instructions r OMB Statement, below.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on FDA's website: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119184.htm

1. APPLICANT'S NAME AND ADDRESS	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
CMP PHARMA INC Ellen Barkley P.O. BOX 147 -- FARMVILLE NC 27828 US	209-478
2. NAME AND TELEPHONE NUMBER OF REPRESENTATIVE 252-753-7111	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? [ ] YES [X] NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: [ ] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION [ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:
3. PRODUCT NAME Carospir (Spironolactone Oral Suspension)	6. USER FEE I.D. NUMBER PD3016299

7. ARE YOU REDEEMING A PRIORITY REVIEW VOUCHER FOR THE TREATMENT OF TROPICAL DISEASES? [ ] YES [X] NO

PRIORITY REVIEW VOUCHER NUMBER:

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.
[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)
[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food,Drug, and Cosmetic Act
[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY

9. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?
[ ] YES [X] NO
a waiver has been granted, include a copy of the official FDA notification with your submission.

Privacy Act Notice:
This notice is provided pursuant to the Privacy Act of 1974, 5 U.S.C. 552a. The collection of this information is authorized by 21 U.S.C. 371, 379, 379e, 379h, 379h-1, 379j, 379j-12, 379j-21, 387s, and 393(d)(2); 42 U.S.C. 263b(r)(1); 5 U.S.C. 301 and 552; and 42 U.S.C. 3101. FDA will use the information to assess, collect and process user fee payments, and, facilitate debt collection under the Debt Collection Improvement Act. FDA may disclose information to courts and the Department of Justice in the context of litigation and requests for legal advice; to other Federal agencies in response to subpoenas issued by such agencies; to HHS and FDA employees and contractors to perform user fee services; to the National Archives and Records Administration and General Services Administration for records management inspections; to the Department of Homeland Security and other Federal agencies and contractors in order to respond to system breaches; to banks in order to process payment made by credit card; to Dun and Bradstreet to validate submitter contact information, and to other entities as permitted under the Debt Collection Improvement Act. Furnishing the requested information is mandatory. Failure to supply the information could prevent FDA from processing user fee payments. Additional detail regarding FDA's use of information is available online:
http://www.fda.gov/RegulatoryInformation/FOI/PrivacyAct/default.htm.

)MB Statement:
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research Office of Information Management (HFA-710) 8455 Colesville Road, COLE-14-14253 Silver Spring, MD 20993-0002	Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research Office of Information Management (HFA-710) 8455 Colesville Road, COLE-14-14253 Silver Spring, MD 20993-0002	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

PRINTED NAME AND SIGNATURE OF AUTHORIZED REPRESENTATIVE	TITLE	DATE
Gerald Sakowski 	CEO	10/03/2016

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$1,019,050.00

Form FDA 3397 (03/16)

Online Payment

Step 3: Confirm Payment 1 | 2 | 3

Thank you.
Your transaction has been successfully completed.

Pay.gov Tracking Information

Application Name: FDA User Fees
Pay.gov Tracking ID: 25U4ISM6
Agency Tracking ID: 3016299
Transaction Date and Time: 09/30/2016 08:15 EDT

Payment Summary

Account Holder Name: CMP PHARMA INC
Payment Amount: $1,019,050.00
Account Type: Business Checking
Routing Number: (b) (4)
Account Number:
Check Number:

Payment Date: 10/03/2016

Reference ID: 4144255

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: March 31, 2019

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable check box.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	Dr. Satya Siva Varaprasad Marrey, M.B.B.S, MPH	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Gerald Sakowski	Chief Executive Officer
FIRM/ORGANIZATION: CMP Pharma, Inc.	
SIGNATURE	DATE *(mm/dd/yyyy)*: 09/28/2016

This section applies only to the requirements of the Paperwork Reduction Act of 1995.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Do NOT send your completed form to the PRA Staff email address below.

Department of Health and Human Services
Food and Drug Administration
Office of Operations
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."