CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209112Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation:
APPROVAL
(including the Overall Manufacturing Inspection Recommendation)

NDA 209112
ADDENDUM TO Review #1

The following comments are specific to the labeling of this product:

The applicant originally proposed the product to be a Pharmacy Bulk Package (PBP) (b) (4)

- The proposal was found to be deficient by FDA because (b) (4) . In response to FDA's information request, the applicant revised the labeling to state that the product is "single dose".

During the final labeling review, FDA found that "single dose" is not appropriate for the product because, as per the final Clinical determination, the (b) (4) daily dose is 200 mg or 0.4 mL, and the excess amount in the product vial containing 50 mL is not acceptable.

- Therefore, the product will be labeled as "Pharmacy Bulk Package" with additional language in the Prescribing Information to state that the unused portion of the vial should be discarded within 4 hours and the diluted product should be used immediately. This revised language is found adequate by both the OND LDT and the OPQ Microbiology team.
- The container and carton labels will be revised to state "Pharmacy Bulk Package".

Application Technical Lead Signature: Suong T. Tran -S

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QUALITY REVIEW

Recommendation: APPROVAL
(including the Facility Review/Overall Manufacturing Inspection Recommendation)

NDA 209112

Review #1
Review Date (see last page)

Drug Name/Dosage Form	ascorbic acid injection
Strength	500 mg/mL (presentation: 25g/50 mL)
Route of Administration	IV injection
Rx/OTC Dispensed	Rx
Applicant	McGuff Pharmaceuticals

SUBMISSION(S) REVIEWED	DOCUMENT DATE
0000	9/2/16
0003	10/5/16
0004	12/14/16
0006	3/8/17
0007	3/10/17
0009	4/21/17
0010	5/19/17
0011	6/12/17
0012	7/6/17

Quality Review Team

DISCIPLINE	REVIEWER	DIVISION/OFFICE
Regulatory Business Process Manager	Anika Lalmansingh	Regulatory Business Process Management I/OPRO
Application Technical Lead	Suong (Su) Tran	New Drug Products II/ONDP
API	Sam Bain/Donna Christner	New Drug API/ONDP
Drug Product	Muthukumar Ramaswamy/ Danae Christodoulou	New Drug Products II/ONDP
Process	Hong Yang/ Yong Hu	Process Assessment II/OPF
Facility	Michael Klapal/Viday Pai	Inspectional Assessment/OPF
Microbiology	Maria Cruz-Fisher/Paul Dexter/ Jesse Wells	Process Assessment II/OPF

Quality Review Data Sheet

1. **RELATED/SUPPORTING DOCUMENTS:**
   A. **DMFs:** Adequate (see Chapter II)
   B. **Other Documents:** none
2. **CONSULTS:** not applicable

Executive Summary

I. Recommendation and Conclusion on Approvability

The final OPQ recommendation is for Approval, including the overall manufacturing inspection recommendation.

II. Summary of Quality Assessment

A. Product Overview

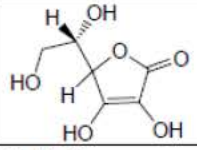
This is a 505(b)(2) application for Ascorbic Acid Injection. The application relies on published literature for information on safety and effectiveness.

The drug substance of this NDA is ascorbic acid.
The drug product is Ascorbic Acid Injection, a sterile, preservative-free solution to be diluted with 5% dextrose or Sterile Water for Injection (b) (4) for intravenous injection. Each 1 mL provides 562.5 mg sodium ascorbate, equivalent to 500 mg ascorbic acid. The product is packaged in a 50 mL vial (containing 25 g ascorbic acid).

Proposed Indication(s)	[not finalized by GRMP goal; see CDTL's memo]
Duration of Treatment	[not finalized by GRMP goal; see CDTL's memo]
(b) (4) **Daily Dose**	[not finalized by GRMP goal; see CDTL's memo]
Alternative Methods of Administration	Ascorbic Acid Injection is diluted with 5% dextrose or Sterile Water for Injection (i.e. (b) (4) dilution) prior to administration.

B. Quality Assessment Overview

Drug Substance

	Chemical Name: (2R)-2-[(1S)-1,2-Dihydroxyethyl]-3,4-dihydroxy-2H-furan-5-one
Structure	
Molecular Formula	$C_8H_8O_6$
Molecular Weight	176.1

The drug substance is Ascorbic Acid. DMF (b) (4) is referenced for all CMC information on the drug substance and is currently adequate.

Drug Product

The drug product is Ascorbic Acid Injection, a sterile, preservative-free solution to be diluted with 5% dextrose or Sterile Water for Injection ((b) (4) dilution;

adequate compatibility data are provided) for intravenous injection. Each 1 mL provides 562.5 mg sodium ascorbate, equivalent to 500 mg ascorbic acid. The product is packaged in a 50 mL vial (containing 25 g ascorbic acid).

The drug product is formulated to have a target concentration of 500 mg/mL. However, ascorbic acid has a solubility limit of 333 mg/mL. Therefore, (b) (4)

Excipients (per mL): (b) (4) edetate disodium, sodium bicarbonate (b) (4) water for injection (b) (4) and sodium hydroxide for pH adjustment to pH 5.6-6.6.

The product manufacturing process consists of (b) (4)

The regulatory drug product specification is based on the USP monograph for the product and the current USP <1> for parenteral products, with the (b) (4) (as per FDA's request, the applicant developed and validated a stability-indicating test method for degradants. The two degradants with limits higher than the applicable ICH qualification threshold (b) (4) (limit of (b) (4)%) and (b) (4) (limit of (b) (4)%). The USP pH criteria are too wide based on data, and the pH criteria for this specific product are finalized to be 5.6-6.6.

Primary container closure system: (b) (4) amber glass vial/bottle, with (b) (4) rubber stopper and (b) (4) cap. The stopper complies with USP <381>, and EP 3.2.9 monograph requirements as well USP <87> and <88> requirements.

Expiration Date & Storage Conditions: 12 months long term storage at 5 °C.

The product is temperature-sensitive; therefore, it cannot be stored at room temperature.

The product lacks an antimicrobial preservative; therefore, the in-use period of the to-be-administered diluted product is limited to four (4) hours.

C. **Special Product Quality Labeling Recommendation**: The Prescribing Information (PI) and container & carton labels include the caution statement "Warning: Pressure may develop within vial upon storage. Exercise care when withdrawing." In addition, the PI includes (b) (4)

D. Life Cycle Knowledge Information/ Final Risk Assessment:

API	page 8 of Chapter I
Drug product	none
Process	none
Facilities	none
Microbiology	none

Application Technical Lead Signature:
I concur with the reviewers' recommendations.

Suong T. Tran -S

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MICROBIOLOGY

Product Background:

NDA: 209112

Drug Product Name / Strength: Ascorbic Acid Injection, USP, 500 mg/mL; packaged in 50 mL/ (b) (4); pharmacy bulk

Route of Administration: I.V.

Applicant Name: McGuff Pharmaceuticals, Inc.

Manufacturing Site:
McGuff Pharmaceuticals, Inc.
2921 W MacArthur Blvd Suite 141
Santa Ana, CA 92704

Method of Sterilization: (b) (4)

Review Summary: The submission **is** recommended for approval on the basis of sterility assurance.

List Submissions being reviewed: 9/2/2016, 12/14/2016, 3/2/2017, 5/19/17

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: none

Supporting/Related Documents:
DMF (b) (4) (Type V; (b) (4)) is referenced for the (b) (4) of the (b) (4). An LOA dated 4/19/2005 is provided. The relevant information was reviewed in the Microbiology Review #33 (document "(b) (4).doc," by M. Cruz-Fisher, dated 2/3/2017) and was deemed adequate.

An LOA dated 2/13/17 for DMF (b) (4) (Type III) is provided. The relevant information was reviewed in the Microbiology Review (b) (4).doc by CAPT Paul L. Dexter, dated 8/2/2017 and was deemed adequate.

Remarks Section: Some of the tables in this review have been copied directly from the submission.

An IR letter (dated 2/7/2017) was sent to the firm with a list of the microbiology deficiencies. The applicant's responses (dated 3/8/2017) are included in the review. An email was sent to the

firm 5/4/17 with microbiology deficiencies. The applicant's responses (dated 5/19/17) are included in this review.

S Drug Substance (DS)

- Not applicable; DS is not sterile.

P.1 Description of the Composition of the Drug Product (DP)

- Description of DP – The subject DP is a sterile, pyrogen-free, aqueous solution.

- DP composition –

Component	Grade	Function	Composition per mL
Ascorbic Acid	USP	Active Ingredient	500 mg
Edetate Disodium (b) (4)	USP	(b) (4)	(b) (4)
Sodium Bicarbonate	USP	(b) (4)	
Sodium Hydroxide	NF	(b) (4) pH adjustment	
Water for Injection	USP	(b) (4)	
			(b) (4)

- Description of container closure system –

Component	Supplier	Address
(b) (4) Glass Vial – Amber color	(b) (4)	(b) (4)
(b) (4) (b) (4) Vial Stopper		
(b) (4)		

Reviewer's Assessment: Example: Acceptable

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity

(b) (4)

(b) (4)

Reviewer's Assessment: Acceptable

Lifecycle Management Considerations

- None related to Microbiology

Reviewer's Assessment: Acceptable

List of Deficiencies: None.

Primary Microbiology Reviewer Name and Date: Maria I. Cruz-Fisher, Ph.D.; 5/11/2017
CAPT Paul L. Dexter, M.S.; 8/02/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed): I concur.
Jesse Wells, Ph.D. 8/02/2017

Maria Cruz-Fisher

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Jesse Wells

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Paul Dexter

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ATTACHMENT I: Final Risk Assessments

See Executive Summary

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