

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209112Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 209112	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Ascor Established/Proper Name: ascorbic acid Dosage Form: injection Strengths: 500 mg/mL		
Applicant: McGuff Pharmaceuticals, Inc.		
Date of Receipt: September 2, 2016		
PDUFA Goal Date: October 2, 2017		Action Goal Date (if different):
RPM: Abolade (Bola) Adeolu		
Proposed Indication(s): treatment of scurvy		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Published literature	Clinical and nonclinical

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature¹. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

The applicant conducted a pharmacokinetic study, MGP-101, entitled “A Phase 1, Single-Dose Study to Evaluate the Pharmacokinetics of Intravenous Ascorbic Acid in Healthy Male and Female Volunteers.”

The submitted literature, including three clinical prospective studies where scurvy was induced in healthy volunteers and multiple case reports of treatment of individuals with scurvy, is scientifically relevant to the proposed product because the studies used the same active pharmaceutical ingredient contained in the Applicant’s drug product. It is not possible to identify enough patients with actual scurvy to do a real study. The doses used in the literature are similar to the proposed doses, that support both the efficacy and safety. Findings from nonclinical studies in the public literature support treatment with adequate safety margins at the proposed doses.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☒ NO ☐
If “NO,” proceed to question #5.

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA’s finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

YES ☐ NO ☒

If “NO”, proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA’s finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☐ NO ☒

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☐ YES ☐ NO ☐

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES ☐ NO ☐

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES ☐ NO ☐

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES ☐ NO ☐

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☐ NO ☐

If “YES”, please list which drug(s) and answer question d) i. below.

If “NO”, proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES ☐ NO ☒

If “**NO**” to (a) proceed to question #11.
If “**YES**” to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

If this application relies only on non product-specific published literature, answer “N/A”

*If “**YES**” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*

*If “**NO**” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO ☒

*If “**NO**”, proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☐ NO ☐

If this application relies only on non product-specific published literature, answer “N/A”

*If “**YES**” and there are no additional pharmaceutical alternatives listed, proceed to question #12.*

*If “**NO**” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in*

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS
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- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

☒ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the*

NDA holder/patent owner, proceed to question #15.

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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/s/

ABOLADE ADEOLU
09/29/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 29, 2017
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 209112
Product Name and Strength:	Ascor (ascorbid acid) injection, 25,000 mg/50 mL (500 mg/mL)
Applicant/Sponsor Name:	McGuff Pharmaceuticals, Inc.
Submission Date:	September 28, 2017
OSE RCM #:	2016-2070-2
DMEPA Team Leader:	Hina Mehta, PharmD
DMEPA Associate Director: (Acting)	Mishale Mistry, PharmD, MPH

1 PURPOSE OF MEMO

The Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised container label and carton labeling, and the proposed packaging for Ascor (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions to the labels and labeling are in response to recommendations that we made during a previous review.^a

2 CONCLUSION

The revised container label and carton labeling for Ascor are acceptable from a medication error perspective. We have no further recommendations at this time.

^a Mehta H. Label and Labeling Review for Ascor (NDA 209112). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Sept 21. RCM No.: 2016-2070-1.

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/s/

HINA S MEHTA
09/29/2017

MISHALE P MISTRY
09/29/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 21, 2017
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 209112
Product Name and Strength:	Ascor (ascorbid acid) injection, 25,000 mg/50 mL (500 mg/mL)
Applicant/Sponsor Name:	McGuff Pharmaceuticals, Inc.
Submission Date:	September 13, 2017
OSE RCM #:	2016-2070-1
DMEPA Team Leader:	Hina Mehta, PharmD
DMEPA Associate Director: (Acting)	Mishale Mistry, PharmD, MPH

1 PURPOSE OF MEMO

The Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised container label and carton labeling, and the proposed packaging for Ascor (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions to the labels and labeling are in response to recommendations that we made during a previous review.^a

2 DISCUSSION

The Applicant proposes an indication for the short term (up to one week) treatment of scurvy in adult and pediatric patients aged 5 months and older for whom oral administration is not possible, insufficient, or contradicted. The dose is as follows:

- Age 5 months to less than 12 months: 50 mg once daily
- Age 1 year to less than ^(b)₍₄₎ years: 100 mg once daily

^a Vee S. Label and Labeling Review for Ascor (NDA 209112). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Mar 15. RCM No.: 2016-2070.

- Adult and pediatric patients age ^(b)₍₄₎ years and older: 200 mg once daily
- Pregnant women, nursing women, patients with glucose-6 phosphate dehydrogenase deficiency: should not exceed the US Recommended Dietary Allowance (RDA)

The maximum duration of the product is one week.

We note that the Applicant proposes to package Ascor in a Pharmacy Bulk Package (PBP) in a strength of 25,000 mg per 50 mL (500 mg/mL) vial. The vial must be diluted prior to use and should be used within 4 hours of puncture.

There are unapproved ascorbic acid products available in the same strength currently available. We conducted a FAERS search of ascorbic acid injection products on September 19, 2017 and did not identify any cases of overdoses.^b

We note a pediatric patient would require a dose of 50 mg. However, taking into consideration the indication of the product, the frequency of administration (once daily) and the vial must be diluted and used within 4 hours of puncture, the majority of the drug product would be wasted if only treating one patient. Therefore, we recommend that the Applicant consider future packaging that takes into account the indication, dose, frequency, and stability for this product to address drug wastage concerns. We provide this recommendation to the Division in Section 4.1.

3 CONCLUSION

The revised container label and carton labeling for Ascor are unacceptable from a medication error perspective. We provide recommendations for the Division regarding the proposed packaging in Section 4.1 and labels/labeling recommendations for the Applicant in Section 4.2.

4 RECOMMENDATIONS

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Proposed Packaging

1. In considering the product indication, dose and frequency, and the need to discard the product 4 hours after vial puncture, we are concerned that the proposed packaging for this product will lead to significant drug wastage. Therefore, we recommend that the Applicant consider packaging the product with a more suitable volume, taking into account the indication, dose, frequency, and stability for this product, as a future consideration.

4.2 RECOMMENDATIONS FOR MCGUFF

A. Carton Labeling and Container Label

^b FAERS Search of Ascorbic Acid with Event PT of Overdose, Accidental Overdose, Intentional Overdose, Prescribed Overdose conducted on Sept 19, 2017.

1. Include the statement "Pharmacy Bulk Package" on the Principal Display Panel (PDP) and remove "Single dose vial, discard unused portion". Ensure that the statement is prominent on the PDP so it is not overlooked.
2. Re-locate the statement "Any unused portion must be discarded within 4 hours" to the PDP to ensure this important information is not overlooked.
3. Add the statement, "Contains no preservative" on the PDP, if space permits, to ensure that this important information is not overlooked.

B. Tray Label

1. Include the statement "Pharmacy Bulk Package" on the PDP and ensure the statement is prominent so it is not overlooked.
2. Move statement "Must dilute before use" to PDP to ensure this important information is not overlooked.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

HINA S MEHTA
09/21/2017

MISHALE P MISTRY
09/21/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memorandum

Date: September 19, 2017 **Date consulted:** September 12, 2016

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, M.D., MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Metabolism & Endocrinology Products (DMEP)

Drug: Ascor (ascorbic acid injection) for intravenous use

Drug Class: Vitamin C

NDA: 209112

Applicant: McGuff Pharmaceuticals Inc. (MPI)

Subject: Pregnancy and Lactation Labeling Rule (PLLR) format

Indication: Ascorbic Acid Injection 500 mg/mL is a vitamin indicated for the treatment of scurvy

Materials Reviewed:

- DPMH consult request dated September 12, 2016, in DARRTS Reference ID 3984466
- NDA 209112 and Prescribing Information (PI) for Ascor (ascorbic acid injection) for intravenous use, submitted September 2, 2016
- Response to Filing Communication on Prescribing Information of December 28, 2016, and revised labeling
- Memorandum of the Pediatric Team of DPMH to ascorbic acid pediatric labeling review by Elizabeth L. Durmowicz, MD

Consult Question:

DMEP requests DPMH assistance with reviewing the applicant's Pregnancy and Lactation Labeling section to comply with PLLR format.

INTRODUCTION

On September 2, 2016, the applicant, McGuff Pharmaceuticals Inc. (MPI), submitted an original New Drug Application (NDA 209112) for Ascor (ascorbic acid injection), for treatment of scurvy in accordance with Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355). This NDA completely relies on published literature, although the drug has been previously marketed without an approved NDA. On September 12, 2016, the Division of Metabolism & Endocrinology Products (DMEP) consulted the Division of Pediatric and Maternal Health (DPMH), to provide input for appropriate labeling of Ascor to comply with the Pregnancy and Lactation Labeling Rule format.

This review provides recommended revisions and structuring of information related to the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections in labeling in order to provide clinically relevant information for prescribing decisions and to comply with current PLLR regulatory requirements.

BACKGROUND

Regulatory History

- MPI's Ascorbic Acid (AA) formulation (Ascorbic Acid Injection, USP) (500 mg/mL) was marketed in the U.S. as Ascor L 500 from 2002 – 2010 (without an approved NDA) and voluntarily withdrew the product to comply with FDA's Unapproved Drug Initiative.
- The AA formulation is currently marketed internationally as Ascor L 500. Per the applicant, Ascor L 500 has marketing authorization for the treatment of scurvy in adults in Canada, New Zealand and Peru, and the approved dosing ranges from 70 mg – 6 grams/day.
- On August 31, 2007, the Office of Orphan Products Development granted Ascorbic Acid Injection an orphan designation (#07-2437) for the treatment of scurvy.
- On August 31, 2016, the applicant submitted NDA 209112 in accordance with Section 505(b)(2) to seek marketing approval for Ascorbic Acid Injection (IV), USP (500 mg/mL) for the treatment of scurvy in adult and pediatric patients.
- AA injection products for intravenous (IV), subcutaneous (SC) and intramuscular (IM) use are available in the U.S. by other drug manufacturers as unapproved drug products for the prevention and treatment of scurvy, and provide dosing recommendations for the treatment of scurvy (i.e., 300 mg to 1 gram daily) in adults.^{1,2}

Ascor Drug Characteristics³

Ascor (ascorbic acid) is Vitamin C, an essential nutrient.¹⁸ The vitamin is an essential coenzyme for collagen formation, tissue repair and synthesis of lipids and proteins. It acts both as a reducing agent and as an antioxidant and is necessary for many physiologic functions, e.g., metabolism of

¹ Durmowicz, EL, Memorandum to Ascorbic Acid for Pediatric Labeling Review

² Review of the DailyMed website available at

<https://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=all&query=ASCORBIC+ACID&audience=consumer> (accessed August 29, 2017) identified five unapproved AA solutions for injection that appear to be marketed in the U.S. Examples include a product sponsored by American Regent, Inc.

(<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=cdc0522c-57f0-488d-b4bb-1a3c35631949>) and a product marketed by Raw Materials International Overseas, LLC (labeling information available at <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1ac7a17e-75d0-4444-e054-00144ff88e88>).

³ Ascor proposed labeling, Sections 11 and 12.

iron and folic acid, resistance to infection, and preservation of blood vessel integrity. The human body lacks the ability to synthesize and produce vitamin C and therefore depends on exogenous dietary sources to meet Vitamin C requirements.^{4,5} Vitamin C is important in making a structural protein, collagen, which is a cartilage component for most tissues and organs such as bones, tendons and skin. Vitamin C also helps the body to absorb iron.

Each mL contains 500 mg of ascorbic acid and sodium bicarbonate (b) (4). The intravenous (IV) administration of ascorbic acid results in rapid absorption, reaching peak levels higher than those observed with oral dosing at doses > 200 mg. Also, the linear PK parameters above these doses were similar.^{6,7}

Ascor has a molecular weight of 176.124 g/mol and a half-life of approximately 30 minutes⁸ to 16 days for not supplemented patients. High oral doses (more than 1000mg/day) of ascorbic acid (vitamin C) have a half-life of 3.4 hours.⁹ Orally administered ascorbic acid (vitamin C) is absorbed by the small intestine and is distributed throughout the extracellular space and concentrated in most tissues. Ascorbic acid (vitamin C) does not accumulate and is excreted via urine after oral doses greater than 500mg /day. The vitamin is excreted by the kidney in large amounts only when the plasma concentration exceeds a threshold, which is approximately 1.4 mg/100 mL. When the body is saturated with ascorbic acid, the plasma concentration will be about the same as that of the renal threshold; if further amounts are then administered, most of it is excreted in the urine. When body tissues are not saturated and plasma concentration is low, administration of ascorbic acid results in little or no renal excretion.¹⁰

Scurvy and Pregnancy

Scurvy is the term for vitamin C deficiency. The disease develops when the total body pool of ascorbic acid is depleted to below 300 mg.⁴ This correlates with serum levels of ascorbic acid (vitamin C) of approximately <0.2 mg/L or 11 µmol/L or that of leukocyte concentrations below 7 mg/L (397 µmol/L).¹ Scurvy can lead to anemia, debility, exhaustion, spontaneous bleeding, pain in the limbs, and especially the legs, swelling in some parts of the body, and sometimes ulceration of the gums and loss of teeth. During pregnancy, ascorbic acid (vitamin C) is essential for wound healing, tissue repair, maintaining skin health and growth of bones. In addition, it helps to fight infections and acts as an antioxidant that protects body cells from any damage.^{11,12,13} Ascorbic acid (vitamin C) deficiency during pregnancy has been reported to

⁴ Bessey, O. A. (1938). Vitamin C: methods of assay and dietary sources. Journal of the American Medical Association, 111, 1290-1298.

⁵ Hodges, R. E., Baker, E. M., Hood, J., Sauberlich, H. E., March, S. C. (1969). Experimental scurvy in man. The American journal of clinical nutrition, 22(5), 535-548.

⁶ Levine, M., Conry-Cantilena, C., Wang, Y., et al (1996 (a)). Vitamin C pharmacokinetics in healthy volunteers: evidence for a recommended dietary allowance. PNAS, 93(8), 3704-3709.

⁷ Levine, M., Wang, Y., & Rumsey, S. C. (1999). Analysis of ascorbic acid and dehydroascorbic acid in biological samples. Methods in enzymology, 299, 65.

⁸ <https://www.ncbi.nlm.nih.gov>

⁹ Hale T. Medications and mothers' milk, 17th Edition, Springer Publishing Co., LLC, 2017

¹⁰ Proposed ascorbic acid injection's labeling, edits by Clinical Pharmacology reviewer Dipak Pisal, Ph.D.

¹¹ Krebs, H. A. (1953). The Sheffield experiment on the vitamin C requirement of human adults. Proceedings of the Nutrition Society, 12(03), 237-246.

¹² Anderson, L. C., Otto, G., Pritchett-Corning, K. R., Whary, M. T. (2015). Laboratory Animal Medicine, 3rd Edition: Elsevier.

¹³ National Research Council 1995. Nutrient Requirements of Laboratory Animals. Fourth Revised Edition, 1995. Subcommittee on Laboratory Animal Nutrition, Committee on Animal Nutrition, Board of Agriculture, National Research Council. National Academy Press, Washington, D.C., 1995.

increase the risk of infections, premature rupture of the membranes,^{14,15} premature birth,^{24,16} and eclampsia.¹⁷ Scurvy is a rare disease that has been diagnosed in severely malnourished individuals, including children five months of age and older with severely restricted diets related to psychiatric or developmental disorders.^{18,19} Infantile scurvy is very rare as formula is fortified with vitamin C and human milk has an adequate supply of the vitamin.²⁰ Ascorbic acid (vitamin C) is actively transported across the placenta.^{21,22}

REVIEW PREGNANCY

Neither *in vitro* nor *in vivo* safety or efficacy testing of ascorbic acid (vitamin C) or Ascorbic Acid Injection, USP drug product was conducted by the applicant in support of this NDA for the treatment of scurvy. Information that is available in the public domain is used to support the proposed dose (b) (4) in treatment of scurvy and for nonclinical and clinical evaluation.

Nonclinical experience

For further details on the review of the published non-clinical information, the reader is referred to the review by the non-clinical reviewer Parvaneh Espandiari, Ph.D.

Based on non-GLP studies in animals, the published literature reports that ascorbic acid (vitamin C) is not genotoxic, teratogenic or carcinogenic at dose levels relevant to the treatment of scurvy.²³ Pregnant guinea pigs fed large dose levels of ascorbic acid (vitamin C) gave birth to offspring with increased rates of ascorbic acid (vitamin C) catabolism.²⁴

Review of Clinical Literature

The applicant relies on published literature for demonstration of the safety and efficacy for use of Ascorbic Acid Injection, USP. The applicant performed a literature search for the use of ascorbic acid or vitamin C use during pregnancy. DPMH also performed a similar search in PubMed. Keywords used relevant to the ascorbic acid or vitamin C in pregnancy include: “Pregnancy, pregnancy outcome, pregnancy complications, pregnant, pregnancies, abortion, induced abortion, spontaneous abortion, miscarriage, embryo implantation, fetal resorption, embryo loss, preterm birth, premature birth, developmental toxicity, skeletal variation, and malformation, birth or

¹⁴ Casanueva, E., Polo, E., Tejero, E., & Meza, C. (1993). Premature rupture of amniotic membranes as functional assessment of vitamin C status during pregnancy. *Annals of the New York Academy of Sciences*, 678(1), 369-370.

¹⁵ Pfeiffer, F., Valdés-Ramos, R., Avila-Rosas, H., Meza, C., & Casanueva, E. (1996). Iron, zinc and vitamin C nutritional status is not related to weight gain in pregnant women. *Nutrition Research*, 16(4), 555-564.

¹⁶ Tlaskal, P., & Novakova, V. (1990). Vitamins C and E in neonates and their mothers. *Ceskoslovenska pediatrie*, 45(6), 339-343.

¹⁷ Jendryczko, A., & Tomala, J. (1995). The total free radical trapping ability of blood plasma in eclampsia. *Zentralblatt für Gynäkologie*, 117(3), 126-129.

¹⁸ Weinstein M, Babyn P, Zlotkin S. An Orange a Day Keeps the Doctor Away: Scurvy in the Year 2000. *Pediatrics*. 2001;108(3)e55. doi: 10.1542/peds.108.3.e55

¹⁹ Grewar

²⁰ IOM 2000

²¹ Hytten, F. E., & Robertson, E. G. (1971). Maternal water metabolism in pregnancy. *Proceedings of the Royal Society of Medicine*, 64(10), 1072.

²² McEvoy, C. T., Schilling, D., Clay, N., et al. (2014). Vitamin C supplementation for pregnant smoking women and pulmonary function in their newborn infants: a randomized clinical trial. *JAMA*, 311(20), 2074-2082.

²³ Final Report of the Safety Assessment of L-Ascorbic Acid, Calcium Ascorbate, Magnesium Ascorbate, Magnesium Ascorbyl Phosphate, Sodium Ascorbate, and Sodium Ascorbyl Phosphate as Used in Cosmetics” by the Cosmetic Ingredient Review Expert Panel published in the *International Journal of Toxicology* (2005)

²⁴ Norkus EP, Rosso P: Effects of maternal intake of ascorbic acid on the postnatal metabolism of this vitamin in the guinea pig. *J Nutr* 111:624-30, 1981.

congenital abnormalities, defects or deformities. In addition, DPMH searched TERIS, Micromedex Solutions²⁵ and Shepard's²⁶ databases for relevant data. Limited publications on Ascorbic Acid Injection were identified. The majority of publications identified were with oral administration.

The upper intake levels (UIL) for ascorbic acid oral dosing is established at 2000 mg/day for adults (IOM 2000).²⁷ It is not known if this high dose of ascorbic acid (vitamin C) applies to specific populations (pregnant and lactating women). The RDA doses for these populations are 80-85mg/day during pregnancy and 115-120mg/day during lactation, while for not pregnant adults (19 years and older) the RDA is 90mg/day for men and 75mg/day for women. Oral doses up to 1000mg/day have been administered to pregnant women without any reports of adverse events, except for two reports in the literature that describe neonatal *conditioned* scurvy occurred after high maternal dietary intake of ascorbic acid (vitamin C) orally during pregnancy. A UIL specific for intravenous dosing has not been defined.

Reviewer comment

The Council for Responsible Nutrition (CRN)²⁸ considers the event of “conditioned scurvy”, scurvy in newborns of mothers taking high dose vitamin C during pregnancy, as unsubstantiated because the publication commonly cited³⁶ was speculative and the supporting data was missing. Oral scurvy due to withdrawal from high vitamin C intakes was reported in another publication by Siegel et al.²⁹ In this publication, the diagnosis was not confirmed, the time to onset was short, and no plasma vitamin C determinations were made to corroborate the diagnosis. In a large trial by Roberts et al.^{26,27} of about 9,500 women who took ascorbic acid (vitamin C) 1,000mg/day, “conditioned scurvy” was not reported. Therefore, “conditioned scurvy” still remains a theoretical risk, (b) (4)

At dose levels of 200 mg (b) (4) (the (b) (4) dose recommended for the treatment of adults with Ascorbic Acid Injection, USP), exposure is similar for both oral and IV administration (i.e., similar mean area under the plasma concentration time curves (AUC)).^{1,30} Approximately 70%–90% of orally administered ascorbic acid (vitamin C) intakes at 30–180 mg/day is absorbed. However, at doses above 1 g/day, absorption falls to less than 50%, and absorbed, unmetabolized ascorbic acid is excreted in the urine.³¹ Adverse effects with IV ascorbic acid administration of less than 500mg/day for vitamin C deficiency have been reported and include lethargy, fatigue, vein irritation, nausea and vomiting. There are 3 cases of renal failure in patients with pre-existing renal disease and 2 cases of hemolysis in patients with G6PD deficiency.^{5,32,33} Hale recommends that “even though intravenous vitamin C has moderately safe profile, it should be avoided in mothers with pre-existing renal impairment, history of kidney stones, G6PD deficiency or paroxysmal nocturnal hematuria”.

²⁵ 2016 Truven Health Analytics Inc

²⁶ 2016 Shepard's: A Catalog of Teratogenic Agents

²⁷ IOM 2000 Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids

²⁸ Vitamin and Mineral Safety 3rd Edition (2013) Council for Responsible Nutrition (CRN) www.crnusa.org

²⁹ Siegel C, Barker B, Kunstadter M. 1982. Conditioned oral scurvy due to megavitamin C withdrawal. *J Periodontol.* 53:453–455.

³⁰ Levine M, Wang Y, Padayatty SJ, Morrow J (2001). A new recommended dietary allowance of vitamin C for healthy young women. *Proc Natl Acad Sci.*, 98, 9842-6.

³¹ Jacob RA, Sotoudeh G. Vitamin C function and status in chronic disease. *Nutr Clin Care* 2002;5:66-74. [

³² Lawton JM, Conway ET, Crosson JT, Smith CL, Abraham PA. Acute oxalate nephropathy after massive ascorbic acid administration. *Arch Intern Med.* 1985;145:950-51

³³ Campbell GD, Steinberg MH, Bower JD. Ascorbic acid-induced hemolysis in G6PD deficiency. *Ann Intern Med.* 1975;82:810

It is not known whether ascorbic acid injection can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Studies have not been conducted with the Ascorbic Acid for Injection, USP product. There is no clinical safety data on the treatment of pregnant women with scurvy utilizing ascorbic acid (vitamin C). A study by Roberts *et al.*³⁴ assessed the effects of antioxidant supplementation with vitamins C and E, initiated early in pregnancy, on the risk of serious adverse maternal, fetal, and neonatal outcomes related to pregnancy-associated hypertension. In this multicenter, randomized, double-blind, placebo controlled trial involving nulliparous women who were at low risk for preeclampsia, women took daily oral supplementation of 1000 mg of vitamin C and 400 IU of vitamin E between the 9th and 16th weeks of pregnancy. A total of 10,154 women underwent randomization. There was no significant difference between the vitamin and placebo groups in the rates of the primary outcome* (6.1% and 5.7%, respectively; relative risk in the vitamin group, 1.07; 95% confidence interval [CI], 0.91 to 1.25) or in the rates of preeclampsia (7.2% and 6.7%, respectively; relative risk, 1.07; 95% CI, 0.93 to 1.24). Rates of adverse perinatal outcomes did not differ significantly between the groups. The authors concluded that Vitamin C and E supplementation initiated in the 9th to 16th week of pregnancy in an unselected cohort of low-risk, nulliparous women did not reduce the rate of adverse maternal or perinatal outcomes related to pregnancy-associated hypertension. In a secondary analysis of the same data by Hauth *et al.*³⁵, the authors concluded that maternal oral supplementation with vitamin C and E did not reduce the occurrence of spontaneous preterm birth. Neonatal outcomes of infants delivering preterm were similar in preterm newborns whose mothers were randomized to oral treatment with vitamin C or E or a placebo.

Ascorbic acid (vitamin C) is present in the fetus in concentrations higher than those in the mother. The vitamin is passively transferred across the placenta as dehydroascorbic acid and converted to ascorbic acid in the fetal compartment.^{36,37} Two reported cases of infantile scurvy has been observed. In both mothers, ascorbic acid (vitamin C) intake averaged more than 400 mg/day during pregnancy. After birth, the infants' apparent rapid metabolism of ascorbic acid (vitamin C) resulted in clinical vitamin C deficiency.³⁸ Adequate intake of ascorbic acid (vitamin C) by pregnant women as per the US RDA (recommended dietary allowances) is 80 mg/day for pregnant women 18 years old and younger and 85 mg/day, for 19 years old or older, [Institute of Medicine (IOM) guidelines]. This recommendation should be followed at all times.¹⁹

³⁴ Roberts JM, Myatt L, Spong CY et al. Vitamins C and E to Prevent Complications of Pregnancy-Associated Hypertension. *N Engl J Med.* 2010; 362(14): 1282–1291.

*The primary outcome was a composite of pregnancy-associated hypertension and serious adverse outcomes in the mother or her fetus or neonate, severe pregnancy-associated hypertension alone or severe or mild pregnancy-associated hypertension with one or more of the following: elevated liver enzyme levels (an aspartate aminotransferase level ≥ 100 U per liter), thrombocytopenia (a platelet count of $<100,000$ per cubic millimeter), elevated serum creatinine level (≥ 1.5 mg per deciliter [$132.6 \mu\text{mol}$ per liter]), eclamptic seizure, an indicated preterm birth before 32 weeks of gestation owing to hypertension-related disorders, a fetus that was small for gestational age (below the 3rd percentile) adjusted for sex and race or ethnic group, fetal death after 20 weeks of gestation, or neonatal death

³⁵ Hauth JC, Clifton RG, Roberts JM, Spong CY et al. Vitamin c and e supplementation to prevent Spontaneous preterm birth. *Obstet Gynecol.* 2010; 116(3): 653–658.

³⁶ Devi SP et al: Serum ascorbate, pyruvate and lactate levels in maternal and cord blood. *Indian Pediatr* 19:229-32, 1982

³⁷ Jee-Lim Choi, Rose RC: Transport and metabolism of ascorbic acid in human placenta. *Am J Physiol* 257:10-3, 1989

³⁸ Cochrane W: Overnutrition in prenatal and neonatal life: a problem? *Can Med Assoc J* 93:893-99, 1965

TERIS reports that “the magnitude of teratogenic risk to child born after exposure to ascorbic acid (vitamin C) during gestation is none” based on limited data. No reduction in the rate of miscarriages has been observed in clinical trials in which vitamin C was administered to pregnant women prior to 20 weeks of gestation.³⁹ No differences in the rates of congenital anomalies were observed between the treated and placebo groups in these studies, but all of these women were treated after 14 weeks gestation.

Applicant’s Pharmacovigilance Database review

On December 28, 2016, the applicant informed the agency that as per the 120 day safety update, there were no new safety information to be reported. The applicant states that MPI maintains a database to track all product and safety related complaints. A query by the applicant of the database from its inception in 2002 reveals no reports of adverse events related to pregnancy.

Discussion

There are published reports on pregnancy exposure to oral ascorbic acid (vitamin C) but no reports on similar exposure with the IV formulation. A large multicenter trial demonstrated that the potential for adverse developmental outcomes risk to a child born after exposure to oral ascorbic acid (vitamin C) during gestation is small. No reduction in the rate of miscarriages or pregnancy induced hypertension has been observed in clinical trials in which ascorbic acid (vitamin C) was administered to pregnant women prior to 20 weeks of gestation. No differences in developmental outcomes have been observed between the treated and placebo groups in these studies, but all of these women were treated after 14 weeks gestation. Vitamin C has been used for many decades without any reported adverse developmental outcomes in pregnancy.

LACTATION

Literature Review

The Applicant and DPMH did not identify any publications of human studies regarding breastfeeding and ascorbic acid (vitamin C) levels in breastmilk following intravenous dosing. However, there are several publications on the effect of ascorbic acid (vitamin C) (from diet and supplements) on ascorbic acid (vitamin C) levels in breastmilk at oral doses up to 1000 mg/day (with estimated bioavailability of approximately 50%).²⁵ Oral ascorbic acid (vitamin C) produces tissue and plasma concentrations that the body tightly controls. Results from pharmacokinetic studies indicate that oral doses of 1.25 g/day ascorbic acid (vitamin C) produce mean peak plasma ascorbic acid (vitamin C) concentrations of 135 micromol/L, which are about two times higher than those produced by consuming 200–300 mg/day ascorbic acid from ascorbic acid (vitamin C) -rich foods.^{40,41}

Byerley and Kirksey⁴² examined the influence of diet and supplementation in 25 lactating women (7-13 weeks post-partum and one woman at 20 weeks postpartum). The women were administered 90 mg of ascorbic acid (vitamin C) for 1 day followed by 250, 500 or 1000 mg/day for 2 days or unsupplemented for 1 day followed by either 0 or 90 mg/day ascorbic acid (vitamin C) supplement for 2 days. Ascorbic acid (vitamin C) content in breast milk and urine was measured. Ascorbic acid (vitamin C) intakes of infants were calculated from breast milk volume and from ascorbic acid (vitamin C) levels in breast milk samples obtained at each feeding. Total

³⁹ Rumbold A, Middleton P, Pan N, Crowther CA: Vitamin supplementation for preventing miscarriage. Cochrane Database Syst Rev (1):CD004073, 2011.

⁴⁰ Padayatty SJ, Sun H, Wang Y, Riordan HD, Hewitt SM, Katz A, Wesley RA, Levine M. Vitamin C pharmacokinetics: implications for oral and intravenous use. *Ann Intern Med* 2004;140:533-7.

⁴¹ http://ods.od.nih.gov/factsheets/vitaminC_health_professional/ from NIH, office of dietary supplements

⁴² Byerley LO and Kirksey A. Effects of different levels of vitamin C intake on the vitamin C concentration in human milk and the vitamin C intakes of breast-fed infants. *The American Journal of Clinical Nutrition*. 1985;41: 665-671.

maternal intakes of ascorbic acid (vitamin C), which exceeded 1000 mg/day or 10-fold the RDA for lactation (120 mg/day), did not significantly influence the ascorbic acid (vitamin C) content in breast milk or the ascorbic acid (vitamin C) intakes of infants. Maternal ascorbic acid (vitamin C) intake was positively correlated ($r = 0.7$) with maternal urinary excretion. The RDA for ascorbic acid (vitamin C) as per IOM are presented in Table 1:

Table 1: Adequate intake of Ascorbic Acid (Vitamin C) at different stages of life as per IOM

Life stage	Age	Males (mg/day)	Females (mg/day)
Infants	0-6 months	40	40
Infants	7-12 months	50	50
Adults	19 years and older	90	75
Pregnancy	18 years or younger		80
Pregnancy	19 years or older		85
Breastfeeding	18 years or younger		115
Breastfeeding	19 years or older		120

Ascorbic acid (vitamin C) concentrations in breast milk ranged from 44 to 158 mg/L but were not correlated significantly to maternal intakes of ascorbic acid (vitamin C). Mean ascorbic acid (vitamin C) intakes of infants was estimated to range between 49 ± 9 and 86 ± 11 mg/day and were not statistically different among the different levels of maternal ascorbic acid (vitamin C) intake (from less than 100mg/day to >1000mg/day). However, intakes tended to be higher in absolute values for infants whose mothers consumed 1000 mg/day ascorbic acid (vitamin C) compared to infants whose mothers consumed less than this amount.

The authors concluded that total maternal intakes of ascorbic acid (vitamin C), which exceeded 1000 mg/day or 10-fold the RDA for lactation (120 mg/day), did not significantly influence the ascorbic acid (vitamin C) content in milk or the estimated ascorbic acid (vitamin C) intakes of infants.

Hale T,⁴³ in Medications and Mother's milk, Briggs G et al (2015)⁴⁴ and Toxnet/LactMed⁴⁵ do not provide any additional information.

There are no data on the effects of ascorbic acid (vitamin C) on milk production.

Applicant's Pharmacovigilance Database review

The applicant states: "A query of the database from its inception in 2002 reveals no reports of adverse events related to lactation".

⁴³ Hale, Thomas. Medications and Mother's Milk: A Manual of Lactational Pharmacology, 17th edition. Hale Publishing, L.P. 2017

⁴⁴ Briggs G, Freeman R, Yaffe S., Tenth Edition, 2015, Philadelphia, PA

⁴⁵ Databases on toxicology, [U.S. National Library of Medicine, National Institutes of Health, Health & Human Services. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT](http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT). The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

Discussion

Ascorbic acid (vitamin C) is present in the human milk. Total maternal oral intake of ascorbic acid (vitamin C), even when it exceeds 1000 mg/day orally or 10-fold the RDA for lactation (120 mg/day), does not influence the ascorbic acid (vitamin C) content in breast milk or the ascorbic acid (vitamin C) intakes of infants. Because of lack of data with intravenous administration and no benefit with higher oral doses, lactating women should be limited to the RDA.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

- No studies have been performed with the IV preparation.
- No reproductive effects have been reported in guinea pigs and rats at doses well above those proposed for the treatment of scurvy with ascorbic acid (vitamin C) in humans.^{46,47}
- A study by Zamah et al⁴⁸ revealed that ascorbic acid (vitamin C) does not alter the pharmacokinetics of ethinyl estradiol and levonorgestrel in oral contraceptives
- Few studies have shown that high intake of antioxidants, including ascorbic acid (vitamin C) was associated with better semen quality but there was no clear dose relationship in moderate to low intake.^{49,50,51}

Summary

Overall, ascorbic acid (vitamin C) at the proposed treatment level for scurvy is not expected to have an adverse effect on fertility. There is no information to be relayed about pregnancy testing, contraception, or fertility. Therefore, 8.3 Females and Males of Reproductive Potential should be omitted.

CONCLUSIONS

There are no prospective and well-controlled trials on the use of Ascorbic Acid Injection, USP during pregnancy to determine a drug-associated risk of adverse developmental outcomes. Ascorbic acid (vitamin C) has been marketed in the US since before 1938. The cumulative review of all publications and abstracts from literature search of ascorbic acid (vitamin C) exposure during pregnancy and lactation did not demonstrate evidence of any adverse developmental outcomes in this long history. No safety issues regarding ascorbic acid (vitamin C) exposure during pregnancy or lactation were identified. There is no available information on the effects of the drug on the breastfed infant or the effects of the drug on milk production.

DPMH revised sections 8.1, 8.2, and 8.3 of labeling for compliance with the PLLR. The below recommendations reflect discussion with the DMEP Nonclinical and Clinical teams. DPMH

⁴⁶ Nandi, B. K., Majumder, A. K., Subramanian, N., & Chatterjee, I. B. (1973). Effects of large doses of vitamin C in guinea pigs and rats. *The Journal of nutrition*, 103(12), 1688-1695.

⁴⁷ Seidenberg, J. M., D. G. Anderson, and R. A. Becker. (1986). Validation of an in vivo developmental toxicity screen in the mouse. *Teratog. Carcinog. Mutagen*, 6, 361-374.

⁴⁸ Zamah NM, Humpel M, Kuhn W, Louton T, Rafferty J, Back DJ. Absence of an effect of high vitamin C dosage on the systemic availability of ethinyl estradiol in women using a combination oral contraceptive. *Contraception* 1993;48: 377

⁴⁹ Mohammed Akmal JQ., Qadri NS. Al-Waili S, Thangal AH, Khelod YS. Improvement in Human Semen Quality After Oral Supplementation of Vitamin C. *Journal of Medicinal Food*. 2006;9(3):440-442.

⁵⁰ Eskenazi B, Kidd SA, Marks AR, Slotter E, Block G, Wyrobek AJ. Antioxidant intake is associated with semen quality in healthy men. *J Med Food*. 2006;9(3):440-2.)

⁵¹ Gual-Frau J, Abad C, Amengual MJ, Hannaoui N, Checa MA, Maynou JR, Lozano I, Nikolaou A, Benet J, García-Peiró A, Prats H. Oral antioxidant treatment partly improves integrity of human sperm DNA in infertile grade I varicocele patients, *Human Fertility*, 2015;18:3, 225-229,

refers to the final NDA action for final labeling.

The Pregnancy and Lactation sections of Ascor labeling were structured to be consistent with the PLLR as follows:

- **Pregnancy, Section 8.1**

- The “Pregnancy” section of Ascor labeling was formatted in the PLLR format to include: “Risk Summary”, “Clinical Considerations” and “Data” sections.

- **Lactation, Section 8.2**

- The “Lactation” section of Ascor labeling was formatted in the PLLR format to include the “Risk Summary”, (b) (4) sections.

- (b) (4)

RECOMMENDATIONS

DPMH has the following recommendations for Ascor labeling.

HIGHLIGHTS

- Pregnancy: Doses exceeding the U.S. RDA of ascorbic acid (vitamin C) for pregnant women should be avoided (2.3, 8.1).
- Lactation: Doses exceeding the U.S. RDA of ascorbic acid (vitamin C) for lactating women should be avoided (2.3, 8.2).

FULL PRESCRIBING INFORMATION: CONTENTS

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on use of ASCOR in pregnant women to inform a drug-associated risk of adverse developmental outcomes; however, use of ascorbic acid (vitamin C) has been used during pregnancy for several decades and no adverse developmental outcomes are reported in the published literature (see Data). There are dose adjustments for ascorbic acid (vitamin C) use during pregnancy (see Clinical Considerations). Animal reproduction studies have not been conducted with ascorbic acid (vitamin C). The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Dose adjustments during pregnancy and the postpartum period

Follow the U.S. Recommended Dietary Allowances (RDA) for pregnant women when considering use of ASCOR for treatment of scurvy [see *Dosage and Administration* (2.3)].

Data

Human Data

There are no available data on use of ASCOR or another ascorbic acid injection in pregnant women. However, a published meta-analysis of randomized studies evaluating a large number of pregnant women who took oral ascorbic acid (vitamin C) (through diet and supplementation) at doses ranging from 500 to 1000 mg/day between the 9th and 16th weeks of pregnancy showed no increased risk of adverse pregnancy outcomes like miscarriage, preterm premature rupture of membranes, preterm delivery or pregnancy induced hypertension when compared to placebo. These data cannot definitely establish or exclude the absence of a risk with ascorbic acid (vitamin C) during pregnancy.

8.2 Lactation

Risk Summary

There are no data on the presence of ascorbic acid (vitamin C) in human milk following intravenous administration in lactating women. Ascorbic acid (vitamin C) is present in human milk after maternal oral intake. Maternal oral intake of ascorbic acid (vitamin C) exceeding the U.S. Recommended Dietary Allowances (RDA) for lactation does not influence the ascorbic acid (vitamin C) content in breast milk or the estimated daily amount received by breastfed infants.

There are no data on the effect of ascorbic acid (vitamin C) on milk production or the breastfed infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ASCOR and any potential adverse effects on the breastfed child from ASCOR or from the underlying maternal condition. Follow the U.S. Recommended Dietary Allowances (RDA) for lactating women when considering use of ASCOR for treatment of scurvy [*see Dosage and Administration (2.3)*].

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/s/

CHRISTOS MASTROYANNIS
09/19/2017

TAMARA N JOHNSON
09/19/2017

LYNNE P YAO
09/20/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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M E M O R A N D U M

From: Elizabeth L. Durmowicz, MD, Medical Officer
Division of Pediatric and Maternal Health Staff (DPMH)
Office of Drug Evaluation IV (ODE IV)

Through: Mona Khurana, MD, Pediatric Team Leader
DPMH, ODE IV

To: Division of Metabolic and Endocrine Products (DMEP)
Office of Drug Evaluation II, Office of New Drugs

Subject: Pediatric Assessment in 505(b)(2) NDA

Applicant: McGuff Pharmaceuticals, Inc. (MPI)

Drug: Ascorbic Acid (AA) Injection¹, United States Pharmacopeia (USP)

Trade Name: **Proposed:** (b) (4)

Indication: **Proposed:** Treatment of scurvy
Approved: None

Dosage Form: 25 g L-Ascorbic Acid/50 mL (500 mg/mL)

Route of Administration: Intravenous (IV) Infusion

¹ Per the Chemistry, Manufacturing and Controls reviewers, the correct non-proprietary drug name should be "sodium ascorbate" for injection; however, the applicant provided a rationale for use of ascorbic acid as the non-proprietary name in their December 14, 2016 submission.

Proposed Dosing:

(b) (4)

Consult Request:

DMEP requested DPMH review the pediatric assessment included in the new drug application (NDA) for (b) (4) and comment on the following:

- Adequacy of the submitted data to support the proposed pediatric dosing of ascorbic acid (AA) for the treatment of scurvy
- Acceptability of extrapolating product safety from adults to pediatric patients
- Pediatric use information in labeling

Materials Reviewed:

- Select Documents Submitted in DARRTS under Pre-Investigational New Drug (PIND) #076483
 - PIND Meeting Minutes (December 14, 2007)
 - PIND Meeting Written Responses (September 22, 2011)
- Select Documents Submitted in DARRTS under New Drug Application (NDA) #209112
 - Applicant submission Sequence# 0000 (September 2, 2016)
 - Ethics Consult Review (October 27, 2016)
 - Filing Communication (November 2, 2016)
 - Applicant submission Sequence# 0004 (December 14, 2016)

(b) (4)

○ Pharmacology/Toxicology Review (August 29, 2017)

I. Background

A. Regulatory History of this Application

On August 31, 2016, the applicant submitted NDA 209112 in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the Act) to seek marketing approval for AA IV, USP (500 mg/mL) for the treatment of scurvy in adults and pediatric patients. The Prescription Drug User Fee Act (PDUFA) date was extended by three months to October 2, 2017 because of new drug quality data submitted 10 months into the review cycle.³

The Office of Orphan Products Development granted Ascor L 500® orphan designation for the treatment of scurvy on August 31, 2007(#07-2437). The Filing Communication for this application issued on November 2, 2016 states that the application is exempt from the Pediatric Research Equity Act (PREA). Therefore, this NDA submission does not include an Agreed initial pediatric study plan and was not required to do so.

B. Summary of the Contents of this Application

The applicant is relying on one phase 1 pharmacokinetic (PK), safety, and tolerability study in healthy adults and PK, safety and efficacy information from the published literature to support this NDA submission. The proposed pediatric use is based on extrapolation of adult IV dosing and safety data and the available published literature on the safety and efficacy of oral AA in the treatment of scurvy in pediatric patients.

The NDA includes a summary of nonclinical data from the published literature. The applicant did not conduct in-vitro or in-vivo safety or efficacy testing of AA or AA Injection, USP given the long history of AA use in the treatment of scurvy. Per proposed product labeling, in vivo assays showed no evidence of mutagenicity, “animal studies” of two-year duration using oral L-Ascorbic acid show no evidence of carcinogenicity, and “animal studies” using high oral doses of L-Ascorbic Acid showed no adult toxic, fetotoxic or teratogenic effects.

³ On June 12, 2017, FDA received a major amendment with Quality drug product data submitted on June 9, 2017 (Sequence # 0011). On June 19, 2017, FDA extended the PDUFA date by three months to October 2, 2017.

C. Drug Product

The product is supplied as a 50 mL, single-use vial. Each mL of AA contains 500 mg of ascorbic acid (equivalent to 562.5 mg of sodium ascorbate) and (b) (4) of edetate disodium (EDTA). Sodium hydroxide and sodium bicarbonate are added for pH adjustment (pH range (b) (4)).⁴

DMEP has identified that the large volume of the vial (50 mL) compared to the proposed (b) (4) may result in dosing errors.

DPMH Comment:

The Nonclinical Overview submitted in this NDA includes a summary of AA nonclinical data the applicant considers relevant. The overview does not appear to include data to support the safety of the excipients used in the applicant's AA product. Per the Pharmacology/Toxicology review for this application, no toxicological concerns regarding excipients, impurities/degradants or leachables/extractables were identified, and the concentration of the excipients, including EDTA, is within the range of the FDA Inactive Ingredient Database drugs.

DPMH is concerned that use of the proposed 50 mL single-use vial may be associated with medication errors resulting in overdose. The 50 mg and 100 mg doses require administration of 0.1 mL and 0.2 mL, respectively, volumes significantly less than the volume in the single-use vial. As such, 10-fold increases in dosing could be anticipated. If the full contents, 25 g, are administered, patients less than two years of age may be at significant risk of toxicity due to their renal immaturity.

DMEP should also consider the risk of exposure to high doses of the excipients, especially EDTA, in pediatric patients secondary to the overdosing risks associated with the large volume of drug product contained in a single-use vial. If the full vial is administered, 12.5 mg of EDTA would be administered and may pose a safety concern related to syncope and hypocalcemia. A safe level of pediatric exposure to EDTA has not been identified; (b) (4) a formulation change (i.e., decrease in the quantity of EDTA from 18.8 mg/vial to 5.4 mg/vial) for Emend® (fosaprepitant), (b) (4) for which off-label use was anticipated. Emend® (fosaprepitant) contained (b) (4) times the level of EDTA that was in Leukine® liquid, a product for IV injection that was withdrawn from the market in 2008 due to an increased number of

⁴ Applicant submission Sequence # 0004, December 14, 2016. Labeling for these products do not provide a recommended age range for use or pediatric dosing.

adverse events (hypotension/syncope) temporally related to the addition of EDTA as a preservative. Leukine® liquid was reformulated to be EDTA free. If the 50 ml IV AA single-dose vial is approved, DMEP should consider labeling to warn of the risks of high levels of EDTA, specifically hypotension and hypocalcemia (for additional information on the potential risks of EDTA, please (b) (4) and the (b) (4)).

If the product is approved as a Pharmacy Bulk Package and, as such, overdosing errors are highly unlikely, DPMH is not concerned about the risk of AA or EDTA overdose in pediatric patients being treated for scurvy and labeling is not needed to warn of these risks.

Although not a pediatric issue, per se, the excess volume in the 50 mL vial may contribute to off-label use. If DMEP is concerned about the apparent wide-spread off-label use of high doses of IV AA, DMEP may wish to limit the volume per vial. DPMH suggests further discussion with Division of Medication Error Prevention and Analysis (DMEPA) colleagues regarding strategies to mitigate the risk of medication errors with use of the proposed 50 mL vial.

D. Related Products

Per the applicant, AA injection, USP, has been marketed in the U.S. since before 1938 (i.e., Cenolate®, Bristol Myers Squibb). The applicant marketed their AA formulation, Ascor L 500®, in the U.S. from 2002 – 2010, and voluntarily withdrew the product to comply with FDA's Unapproved Drug Initiative to remove unapproved drugs from the market. AA injection products for IV, subcutaneous (SC) and intramuscular (IM) use are available in the U.S. by other applicants as unapproved drug products for the prevention and treatment of scurvy. Labeling for these marketed unapproved drug products contains dosing recommendations for the treatment of scurvy (i.e., 300 mg to 1 gram daily) in adults only. Per the applicant, Ascor L 500® has marketing authorization for the treatment of scurvy in adults in Canada, New Zealand, and Peru, and the approved dosing ranges from 70 mg – 6 g/day.

DPMH Comment:

This reviewer retrieved labeling information from DailyMed for five unapproved AA injection solutions for IV, IM and SC use in the U.S.⁵ and found labeling content to in general be similar for all five products. The retrieved labeling for all five products provides general dosing recommendations for the treatment of scurvy, but none include pediatric-specific dosing recommendations.

This reviewer retrieved approved labeling for Ascor L 500® from two of the three countries in which this product has been approved for treatment of scurvy⁶ to determine if the ex-U.S. labeling contains pediatric use information. Approved Ascor L 500® labeling identified by the DPMH reviewer from Canada⁷ and from New Zealand⁸ do not provide specific dosing for pediatric patients. Despite lacking clear pediatric dosing recommendations, the New Zealand labeling provides the Recommended Daily Allowances (RDAs) for children and adults, and states that “it is difficult to establish an exact dosage of ascorbic acid suitable for the treatment of deficiencies. In general, therapeutic doses should substantially exceed the recommended daily allowances for health persons”. DPMH reviewers were not able to find the approved Ascor L 500® labeling from Peru.

The applicant provides pediatric dosing information for another AA IV preparation, Pascorbin®, approved for the treatment of scurvy in Germany. The applicant states that their dosing is “still in keeping with the ranges” approved for “other approved products” and provides Pascorbin® as an example. DPMH was not able to obtain Pascorbin labeling to review the recommended pediatric dosing for this product (see Section II A).

⁵ Review of the DailyMed website available at <https://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=all&query=ASCORBIC+ACID&audience=consumer> (accessed August 29, 2017) identified five unapproved AA solutions for injection that appear to be marketed in the U.S. Examples include a product applicant by American Regent, Inc. (<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=cdc0522c-57f0-488d-b4bb-1a3c35631949>) and a product marketed by Raw Materials International Overseas, LLC (labeling information available at <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1ac7a17e-75d0-4444-e054-00144ff88e88>).

⁶ Based on information provided by the applicant

⁷ McGuff Medical Canada, Inc Web site <http://www.mcguiff.ca/>. Package Insert. Accessed August 29, 2017

⁸ New Zealand Datasheet available at <http://www.medsafe.govt.nz/Profs/Datasheet/a/ascorlinj.pdf>. Accessed August 29, 2017

E. Overview of AA (vitamin C)

Vitamin C refers to both AA and dehydroascorbic acid (DHA).⁹ AA is the functional and primary in vivo form of the vitamin.¹⁰ Vitamin C is an essential nutrient for humans and is important in the maintenance of intercellular connective tissues, osteoid, dentine and collagen.¹¹

Oral bioavailability of AA is increased at lower doses (see Table 1) compared to higher doses, and bioavailability is greater in subjects with low plasma AA concentrations.¹²

Table 1: Oral bioavailability and plasma concentration based on dose¹³		
Dose (mg/day)	Bioavailability	Mean Plasma Concentration μM/L (men)
30	87%	9
100	87%	56
200	72%	75
500	63%	NR*
1250 mg	< 50%	NR*
NR: Not reported. Authors note that doses greater than 500 mg/day contribute little to plasma or tissue stores.		

Intravenous administration of AA results in higher peak plasma levels (e.g., 1000 μ M/L after administration of 1.25 gm of AA IV) compared to those that can be attained after oral administration.¹³ Per the applicant, data characterizing the PK of IV AA or data comparing the relative bioavailability of oral and IV AA are not available in pediatric patients.

DPMH Comment:

Per the applicant, the exposure (i.e., Area under the Curve) of AA oral and IV doses is similar in adults for doses (b) (4) based on the literature. However, this statement does not appear to be supported by data from at

⁹ When discussing scurvy and oral intake, the literature generally refers to vitamin C. In this review, DPMH has used the term vitamin C as used in the reference source, and typically reserved the term ascorbic acid (AA) when referring to pharmacological replacement of the vitamin.

¹⁰ Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. National Academies Press, Washington, DC, 2000.

¹¹ Agarwal A, Shaharyar A, Kumar A, Bhat MS, Mishra M. Scurvy in pediatric age group e A disease often forgotten? *J of Clinical Orthopaedics and Trauma*. 2015;6(2):101-107.

¹² Padayatty SJ, Levine M. Vitamin C: the known and the unknown and Goldilocks. *Oral Dis*. 2016;22(6):463-93. doi: 10.1111/odi.12446. Epub 2016 Apr 14. (link)

(b) (4)

least one publication summarizing available PK data for AA that states the bioavailability of

(b) (4)
(b) (4)

DPMH defers the interpretation of the available adult AA IV PK and relative bioavailability data to the Clinical Pharmacology Reviewers but notes that similar data are not included in this NDA submission for pediatric patients.

Without pediatric PK data for AA IV, the relative systemic exposure of oral and IV AA administration of AA in pediatric patients is unknown. In general, for systemically active drugs, supportive pediatric PK are required to support dosing.

F. Overview of Scurvy

Scurvy is caused by dietary deficiency in ascorbic acid and, depending on existing body stores, can occur after 8-12 weeks of inadequate vitamin C intake.¹⁴ The spectrum of the disease is broad and signs and symptoms include dermatologic (e.g., ecchymoses, petechiae), dental (e.g., bleeding, loose teeth), bone (e.g., growth plate fracture, pain) and systemic manifestations (e.g., fatigue).^{15,16} Scurvy is a rare disease that has been diagnosed in severely malnourished individuals, including children five months of age and older with severely restricted diets related to psychiatric or developmental disorders.^{16, 17} Infantile scurvy is very rare as formula is fortified with vitamin C and human milk has an adequate supply of the vitamin.¹⁸

Treatment of scurvy involves AA replacement, usually orally, and supportive care. Infants and children are usually treated with AA 100–300 mg daily and adults 500–1000 mg daily for one month or until full recovery of clinical signs and symptoms occurs. Per the literature, the dose and duration of AA should be individualized.¹⁹ Vitamin C replacement results in improvement of spontaneous bleeding and

¹⁴ Weinstein M, Babyn P, Zlotkin S. An Orange a Day Keeps the Doctor Away: Scurvy in the Year 2000. *Pediatrics*.2001;108(3):e55. doi: 10.1542/peds.108.3.e55

¹⁵ Agarwal A, Shaharyar A, Kumar A, Bhat MS, Mishra M. Scurvy in pediatric age group e A disease often forgotten? *J of Clinical Orthopaedics and Trauma*. 2015;6(2):101-107.

¹⁶ Weinstein M, Babyn P, Zlotkin S. An Orange a Day Keeps the Doctor Away: Scurvy in the Year 2000. *Pediatrics*.2001;108(3):e55. doi: 10.1542/peds.108.3.e55

¹⁷ Grewar D. Infantile Scurvy. *Nutrition*. 1965;4(2):82-89.

¹⁸ Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. National Academies Press, Washington, DC, 2000.

¹⁹ Weinstein M, Babyn P, Zlotkin S. An Orange a Day Keeps the Doctor Away: Scurvy in the Year 2000. *Pediatrics*.2001;108(3):e55. doi: 10.1542/peds.108.3.e55

constitutional symptoms in a few days and improvement in bone abnormalities after several weeks of treatment.²⁰ Untreated, scurvy can be fatal.

II. DPMH Discussion

A. Adequacy of the Submitted Data to Support the Proposed Pediatric Dosing

The applicant is proposing dosing for the following pediatric age groups:

(b) (4)

The applicant has not provided adequate information or scientific justification to support the proposed dosing in pediatric patients. Although the applicant provides information about several considerations used to determine dosing, the applicant does not clearly articulate how they identified the proposed pediatric dose cohort age ranges or how the dose (b) (4) for each of the cohorts were determined. In addition, the applicant has not provided guidance on how clinicians (b) (4)

(b) (4)
(b) (4)
(b) (4) DPMH recommends removing (b) (4)
(b) (4)

To support the efficacy of IV AA in the treatment of scurvy in adult and pediatric patients, the NDA submission includes a review of five observational/controlled studies on the treatment of scurvy or AA deficiency in adults, a summary of a retrospective review of pediatric patients with scurvy (N=28 cases)²² and case reports (n=29 adult cases, n=21 pediatric cases).

²⁰ Agarwal A, Shaharyar A, Kumar A, Bhat MS, Mishra M. Scurvy in pediatric age group e A disease often

(b) (4)

²² Ratanachu-Ek S, Sukswai P, Jeerathanyasakun Y, Wongtapradit, L. Scurvy in pediatric patients: a review of 28 cases. *Journal of the Medical Association of Thailand*. 2003;86,:S734 ([link](#)).

Per the applicant, the literature suggests that low dose treatment (i.e., 10 mg/day orally in adults) is effective,²³ but results in a prolonged rate of recovery and dosing is usually based on severity. The pediatric case reports provided by the applicant reported treatment with 100 mg – 1,000 mg oral AA. Oral pediatric dosing reported in most case reports and provided in the literature is generally 100 - 300 mg per day for all pediatric age groups for one month or until full recovery (see Appendix C). Pediatric dosing guidelines and resources, such as the Harriet Lane Handbook,²⁴ Up to Date^{®25} and Micromedex Solutions[®],²⁶ generally recommend 100 – 300 mg AA/day administered orally, IV, PO or SC, with IM noted to be the preferred route of parenteral administration.

Per the applicant, duration of AA treatment appears to be based on severity of symptoms and that treatment should be continued until resolution of clinical signs and symptoms, usually 1-2 weeks up to 1-3 months. The proposed labeling states that

(b) (4)

. The proposed labeling does not specify the AA formulation that should be used (b) (4).

DPMH's search of the literature found the following:

- No data characterizing the PK of IV AA in pediatric patients
- Guidelines for the oral treatment of scurvy in adults and pediatric patients appear to be based primarily on limited data and clinical experience (see Appendix C).
- Commonly used pediatric dosing resources such as the Harriet Lane Handbook, Up to Date[®] and Micromedex Solutions[®] either do not cite references to support the oral pediatric dosing they recommend or the references cited do not provide robust data to support the recommended oral dosing.
- No data comparing the relative bioavailability of oral and IV AA dosing in pediatric patients.
- No data to support that scurvy occurs in patients less than five months of age

DPMH recognizes there is time and extent of use of this product in pediatric patients but is unable to identify any published data supporting the safety of the applicant's

²³ Krebs HA. The Sheffield Experiment on the Vitamin C Requirement of Human Adults. *Lind Bicentenary Symposium*. 1953;12:237-246.

²⁴ Custer JW, Rau RE. eds. *The Harriet Lane Handbook*. 18th ed. Philadelphia, PA: Elsevier Mosby; 2009. 738.

²⁵ Up to Date. <https://www.uptodate.com/contents/overview-of-water-soluble-vitamins?source=machineLearning&search=scurvy&selectedTitle=1~48§ionRank=1&anchor=H54#H54> Accessed August 30, 2017.

²⁶ Micromedex Solutions[®] 2.0, (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: <http://www.micromedexsolutions.com/> [direct link](#) (Accessed August 29, 2017).

proposed pediatric dosing of IV AA for the treatment of scurvy. The proposed pediatric doses (b) (4)

DPMH recommends limiting the (b) (4) daily AA dose in all proposed pediatric age groups to approximate that currently approved for multivitamin infusion products (see Table 2).

Table 2: IV AA Pediatric Dosing Considerations				
Age Group	Applicant's Proposed Dosing	DMEP Proposed Dosing ¹	DPMH Proposed Dosing ²	Approved AA Dose for Multivitamin Infusion Products ²⁷
5 months ² -12 months	(b) (4)	50 mg once daily	50 mg/once daily	80 mg/day
1 year to 3 years		100 mg/day once daily	100 mg/once daily	80 mg/day
4 years to 10 years		200 mg/once daily. Dose may be repeated as necessary.	100 mg/once daily	80 mg/day
11 years and older		200 mg/once daily. Dose may be repeated as necessary.	200 mg/once daily	200 mg/day
¹ Proposed dosing based on draft labeling sent to the applicant on September 8, 2017.				
² Data to support the safety of repeating the daily dose in pediatric patients are not available. Repeat dosing in patients 11 years and older is reasonable given the likely similarities between adolescent patients and adults (see Section B, DPMH discussion of safety)				
² The applicant's proposed dosing age group is (b) (4)				

DPMH recommends labeling this product for use in patients 5 months of age and older because scurvy is unlikely to be diagnosed in patients less than 5 months of age.

Given that the absorption, distribution, metabolism and excretion (ADME) of IV AA is not likely to be different in adolescent patients compared to adults, recommending the same dosage for adolescents and adults seems reasonable.

²⁷ M.V.I. Pediatric® (NDA 018920) and Infuvite Pediatric (NDAs 021265 & 021646), multiple vitamins for injection products, are approved for maintenance dosage and prevention of vitamin deficiency, respectively, in pediatric patients up to 11 years receiving parenteral nutrition. Dosing is weight based. Data on which the pediatric dosing regimen was determined is not provided in product labeling. No other pediatric parenteral nutrition formulations identified.

The proposed dosing in pediatric patients one year to (b) (4) is within the recommended pediatric dosing range provided in most clinical practice dosing guidelines (i.e., 100-300 mg/day); however, these guidelines do not appear to address the potential for increased AA exposure in patients less than two years of age due to renal immaturity. The (b) (4) in the applicant's proposed dosing (b) (4)

(b) (4)

(b) (4)

(b) (4)

Given the renal immaturity of patients six months to 12 months of age and the unclear exposure-toxicity relationship with IV AA, DPMH recommends a more conservative dosing approach for this age group. Based on experience in this age group with the approved AA daily dose of parenteral multivitamin infusion products (i.e., 80 mg/day), DPMH recommends that IV AA dosing not exceed 80 mg/day for patients five months to 12 months of age.

DPMH does not recommend repeat dosing in patients less than 11 years of age. If DMEP approves the (b) (4) mg once daily dose in patients (b) (4) to less than 11 years of age and allows repeat dosing, not only will a one-time dose (b) (4) (b) (4), but an additional dose will (b) (4) (b) (4). Since the proposed labeling (b) (4), patients (b) (4) to less than 11 years may be administered doses (b) (4) (b) (4)

(b) (4)

B. Extrapolation of Safety from the Adult Data

The applicant states that they reviewed the safety data available in the public domain and considered diverse patient populations, dosing frequency, routes of administration, non-clinical data and relevant pharmacological data. Section 2.7 of the original NDA submission (Sequence # 0000) summarizes safety data from the applicant's Phase 1 PK study (MGP101), three studies in adult patients with advanced

cancer,^{28, 29, 30} one study in adult patients with sepsis,³¹ a summary review of IV AA use in adults by alternative medicine practitioners³² and a study of oral AA use to prevent upper respiratory infection (URI) in pediatric patients.³³ These data provided by the applicant from studies evaluating administration of supraphysiologic doses of IV AA for a diverse number of conditions suggest that high doses of AA administered IV are relatively safe in adult patients without preexisting renal disease or G6PD deficiency. Excess vitamin C intake or administration may put patients with renal disorders at increased risk of oxalate nephropathy and patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency at increased risk for hemolysis. Proposed labeling includes information about these risks.

Despite the favorable safety profile of AA in adults, these safety data cannot be extrapolated to pediatric patients in whom unique susceptibilities to toxicity may exist. For instance, patients less than 2 years of age may be more susceptible to AA toxicity because of their renal immaturity. Because AA is excreted via glomerular filtration, excretion may be decreased (and systemic AA exposures increased) in these patients. The resultant higher AA exposures may increase the risk of oxalate nephropathy after AA administration.

The safety of a drug administered orally cannot be assumed equivalent to the safety of the drug administered IV without bridging bioequivalence data and/or PK data.

If the PK parameters of a drug and exposure-response relationship are expected to be the same in adolescents and adults, and a drug has a low risk safety profile based on time and extent of use, one may expect the safety profile in adolescent patients to be similar to that in adults. Hence, DPMH does not anticipate that adolescents will be at greater risk of adverse reactions with (b) (4) use compared to adults.

The applicant does not appear to have conducted a systematic review of the literature to assess the safety and tolerability of AA IV administered to pediatric patients but

²⁸ Hoffer LJ, Levine M, Assouline S, et al. Phase I clinical trial of i.v. ascorbic acid in advanced malignancy. *Annals of Oncology*. 2008. doi:10.1093/annonc/mdn377

²⁹ Nielsen TK, Hojgaard M, Andersen JT, Poulsen HE, Lykkesfeldt J, Mikines KF. Elimination of Ascorbic Acid After High-Dose Infusion in Prostate Cancer Patients: A Pharmacokinetic Evaluation. *Basic & Clinical Pharmacology & Toxicology*. 2015;116:343–348.

³⁰ Stephenson CM, Levin RD, Spector T, Li, CG. Phase I clinical trial to evaluate the safety, tolerability, and pharmacokinetics of high-dose intravenous ascorbic acid in patients with advanced cancer. *Cancer chemotherapy and pharmacology*. 2013;72(1):139-146.

³¹ Fowler AA, Syed AA, Knowlson S, et al. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. *Journal of Translational Medicine*. 2014;12:322014

³² Padayatty SJ, Sun AY, Chen Q, Espey MG, Drisko J, Levine M. Vitamin C: Intravenous Use by Complementary and Alternative Medicine Practitioners and Adverse Effects. 2010. PLoS ONE 5(7): e11414. doi:10.1371/journal.pone.0011414

³³ Ludvigsson J, Hansson LO, Tibbling G. Vitamin C as a Preventive Medicine against Common Colds in Children. *Scand J Infect Dis*. 1977;9:91-98.

did include a summary of the following published studies with pediatric safety data in their submissions to this NDA:

- A randomized, controlled double-blind study evaluated premature infants (n=119) who were given (1) standard AA dose (i.e., 10/mg/kg/day AA); (2) standard AA dose (i.e., 10/mg/kg/day AA) for ten days, followed by a high AA dose (i.e., 30 mg/kg/day AA); or (3) high dose AA (i.e., 30/mg/kg/day AA) treatment for four weeks. Patients receiving parenteral feedings received IV AA and patients on enteral feeds received oral AA supplementation. Per the authors, no findings suggested that high dose AA, administered oral or IV, was harmful.³⁴
- A case report of a nine-month-old with known G6PD deficiency who developed acute hemolytic anemia after treatment with AA IV 2,000 mg every four hours.³⁵ Per the author of the case report publication, doses of AA that have caused hemolysis in children with G6PD deficiency range from 3-4 grams.
- A clinical study that evaluated oral AA in the prevention of upper respiratory tract infections in patients 8 to 9 years of age. In the pilot study, 172 patients were administered 1,000 mg AA daily for seven weeks and in the “main” study, 642 patients were administered 1,000 mg AA daily for three months. Reported adverse events (AEs) included stomach pains, skin rash, headache, diarrhea and nausea. The applicant reports that AEs were reported in “about” 3% of patients and resulted in study withdrawal in five patients. The authors state that “side effects” were “few and slight”.³⁶ DPMH was not able to determine the exact number of patients that withdrew from the study or the rate of AEs based on the information published.
- A study which evaluated 3,000 mg AA administered orally in conjunction with high doses of niacinamide, calcium and pyridoxine in 41 patients 7 to 11 years of age with attention deficit disorders. Adverse events reported included nausea and vomiting, and elevated transaminase levels up to 171 International Units per liter (IU/L) (n=17, 42% of patients). The authors posited that the elevated transaminases may be related to the niacinamide.³⁷

³⁴ Darlow BA, Buss H, McGull F, Fletcher L, Graham P, Winterbourn CC. Vitamin C supplementation in very preterm infants: a randomized controlled clinical trial. *Arch Dis Child Fetal Neonatal Ed.* 90:F117–F122. doi: 10.1136/adc.2004.056440

³⁵ Huang YC1, Chang TK, Fu YC, Jan SL. C for colored urine: acute hemolysis induced by high-dose ascorbic acid. *Clin Toxicol.* 2014;52(9):984. doi: 10.3109/15563650.2014.954124. ([link](#))

³⁶ Ludvigsson J, Hansson LO, Tibbling G. Vitamin C as a Preventive Medicine against Common Colds in Children. *Scand J Infect Dis.* 1977;9:91-98.

³⁷ Haslam RH, Dalby JT, Rademaker AW. Effects of Megavitamin Therapy on Children with Attention Deficit Disorders. *Pediatrics.* 1984. 74 (1): 103-111.

This DPMH reviewer searched PubMed³⁸ for additional publications describing adverse reactions with AA use and identified two publications reporting on high dose AA administered IV to pediatric patients (n.b., the search did not identify the case report of the nine month old with hemolytic anemia after IV AA treatment). These publications included:

- A report of a randomized, placebo controlled study of the use of 3 g AA administered IV once to improve endothelial function in 19 patients, ages 3.0 to 14.7 years, with a history of Kawasaki disease.³⁹ The publication did not discuss AEs or tolerability.
- A case report on the use of AA IV in the treatment of an optic pathway glioma in a 5 year old patient with neurofibromatosis.⁴⁰ The publication did not discuss AEs or tolerability.

This DPMH reviewer also reviewed a double-blind study in which “high-risk premature” infants (n=51) with birth weight < 1,500 gm were randomized to normal saline (NS) or to IV AA 100 mg/kg/day (in addition to routine parenteral nutrition that contained AA) for seven days. No significant differences in RBC abnormalities or other parameters were identified between the control and high dose AA cohorts.⁴¹

The data from the two studies in premature infants suggest that high doses of IV AA are well-tolerated in premature infants despite their renal immaturity and help support the safety profile of IV AA in older pediatric patients with mature renal function.

This DPMH reviewer reviewed the two references cited by the 2000 Institute of Medicine Dietary Reference Intake report⁴² regarding the association of hemolysis after AA administration in otherwise healthy preterm infants.

³⁸ PubMed was searched on August 31, 2017 using terms “High dose intravenous vitamin C and Children”, “High Dose IV vitamin C AND Children”; “High Dose IV ascorbic acid AND Children”; “High Dose intravenous ascorbic acid AND Children”. Additional searches with substitution of the term “children” with “pediatric”, and the term “IV” and “intravenous” with “parenteral” did not identify additional publications. Five unique publications were identified; three were determined to be not relevant after review of abstract or full text review as IV AA not administered. Review of bibliographies of the three relevant articles and the case report of hemolysis in a nine month old infant by Huang, et al. did not identify additional relevant references.

³⁹ Deng YB, Li TL, Xiang HJ, Chang Q, Li CL. Impaired endothelial function in the brachial artery after Kawasaki disease and the effects of intravenous administration of vitamin C. *Pediatr Infect Dis J*. 2003 22(1):34-9.

⁴⁰ Mikirova N, Hunnughake R, Scimeca RC, et al. High-Dose Intravenous Vitamin C Treatment of a Child with Neurofibromatosis Type 1 and Optic Pathway Glioma: A Case Report. *Am J Case Rep*. 2016;24;17:774-781.

⁴¹ Bass WT, Malati N, Castle MC, et al. Evidence for the safety of ascorbic acid administration to the premature infant. *Am J Perinatol*. 1998;15:133-40.

⁴² Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. National Academies Press, Washington, DC, 2000

- In 1975, Mentzer and Collier published a case report of hydrops fetalis in a 38 week infant after maternal ingestion of fava beans and AA daily for two weeks.⁴³ The authors posit that the infant may have been G6PD deficient. Given that the report does not describe AA administration to a premature infant, the report does not appear relevant.
- In 1988, Ballin et al published results from an in vitro study evaluating the number of Heinz bodies in red blood cells (RBCs) from preterm infants, term infants and adults after incubation in sodium ascorbate. Per the authors, RBCs from premature infants demonstrated increased numbers of Heinz bodies compared to those in term infants and adults, and these findings occurred at sodium ascorbate exposures in vitro that are similar to those that occur in vivo after routine administration of AA. The authors concluded that the evidence suggest that AA places the RBCs of premature infants at risk of oxidative damage.⁴⁴

The data supporting the 2000 IOM Dietary Reference Intake report is weak and does not appear to [REDACTED] (b) (4)

[REDACTED]. DPMH suggests that this information be removed from labeling (see Section D Recommendations, below).

The applicant reports (Section 2.7.4.6 of the original NDA, Sequence # 0000) that during the period of Ascor L 500® marketing in the U.S. (i.e., 2002-2010), no serious or unexpected AEs were reported to MPI related to the use of Ascor L 500® or other AA injection, USP products. The applicant states that MPI has not received any reports of AEs from New Zealand (product approved 2010), Canada (product approved 2010) or Peru (product approved 2015) since commercial distribution commenced in those countries. Given the wide spread availability of AA IV preparations and apparent frequent use for the treatment of many conditions, these postmarketing safety data are reassuring and do not appear to identify an unexpected safety concern.

If postmarketing data are available from other countries that have AA IV preparations that are labeled and provide dosing for the treatment of scurvy in pediatric patients, these data may support the safety of the proposed labeling for [REDACTED] (b) (4)

⁴³ Mentzer WC, Collier E.. Hydrops fetalis associated with erythrocyte G-6-PD deficiency and maternal ingestion of fava beans and ascorbic acid. *J Pediatr*. 1975;86:565–567.

⁴⁴ Ballin A, Brown EJ, Koren G, Zipursky A. Vitamin C-induced erythrocyte damage in premature infants. *J Pediatr*. 1988. 113:114–120

C. Conclusions

DPMH has identified several deficiencies in this NDA with regards to the pediatric assessment. The applicant has not submitted adequate scientific justification to support the safety and efficacy of the proposed pediatric use.

The applicant has not provided any pediatric efficacy data supporting the proposed IV pediatric doses to treat scurvy, and is instead proposing to extrapolate efficacy of IV AA from adults to pediatric patients. While efficacy extrapolation may be reasonable if the pathogenesis of scurvy and response to treatment is expected to be similar between adults and pediatric patients, pediatric dosing and safety cannot be extrapolated.

The data submitted are not only inadequate to support the proposed dosing in the proposed age cohorts, but also do not support the proposed (b) (4), the proposed dosing age cohorts and dosing pediatric patients (b) (4).

Concern has been raised of “conditioned scurvy”, scurvy in newborns of mothers taking high dose vitamin C during pregnancy; however, the data supporting this condition have not been substantiated. Given that scurvy has not been reported in patients less than five months of age and is unlikely to be diagnosed in these infants, pediatric labeling should limit IV AA use to pediatric patients five months of age and older.

Although the minimal effective dose for the treatment of scurvy in adult and pediatric patients is unknown, the literature supports that doses less than the RDA are adequate to treat scurvy and suggest that the approved AA dosing in parenteral nutrition products would be effective in the treatment of scurvy.

Despite the favorable safety profile of AA in adults, adult safety data cannot be extrapolated to pediatric patients in whom unique susceptibilities to toxicities may exist. For instance, patients less than two years of age may be more susceptible to AA toxicity because of their renal immaturity. Because AA is excreted via glomerular filtration, excretion may be decreased (and systemic AA exposures increased) in these patients. The resultant higher AA exposures may increase the risk of toxicities, including oxalate nephropathy, after AA administration. As such, the risk of oxalate nephropathy in patients less than two years of age should be included in labeling.

Given that the PK parameters and the exposure-response relationship of IV AA are expected to be the same in adolescents and adults, and that AA has a low risk safety profile based on time and extent of use, one may expect the safety profile in adolescent patients to be similar to that in adults. Clinical trial data in premature infants administered IV AA did not identify a safety concern. These data suggest that high doses of IV AA are tolerated in premature infants, despite their renal immaturity, and may provide support for the safety profile of IV AA in older pediatric patients.

Postmarketing safety data of currently approved multivitamin infusion products may be leveraged to support the safety of IV AA; however, these postmarketing safety data will not adequately represent the safety of IV AA in pediatric patients. This is because the applicant is proposing (b) (4)

If DMEP considers time and extent of use adequate to support product approval, then DPMH recommends limiting the (b) (4) in all proposed pediatric age groups to approximate that currently approved for multivitamin infusion products; the pediatric experience with IV AA in the approved parenteral nutrition products could then support the safety of the labeled dosing in these products.

Although repeat dosing (i.e., repeat administration of the dose in approved multivitamin infusion products) is unlikely to pose a safety risk in pediatric patients 11 years and older, repeat dosing in younger pediatric patients should not be permitted. Not only would repeat dosing (b) (4)

The proposed pediatric labeling has deficiencies. The Pediatric Use subsection of labeling must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population.⁴⁵ Labeling should adequately convey to prescribers what is known and unknown about use of the drug in the pediatric population. For products with pediatric indications, the pediatric information must be placed throughout labeling as required by 21 CFR 201.57(c)(9)(iv).

⁴⁵ Draft Guidance for Industry and Review Staff: Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling, February 2013

The applicant's proposed labeling statement, (b) (4)
(b) (4)
(b) (4) is not supported by the literature.

The proposed 50 mL single-use vial contains 25,000 mg of L-ascorbic acid and 12.5 mg of EDTA. The AA single-use vial contains a significant volume beyond what would be considered a usual or (b) (4) dose, and, as such is not in accordance with FDA Guidance.⁴⁶ The large amount of AA contained per single-use vial poses the potential for overdose, especially if the full vial is administered. Given that lower AA doses (and as such smaller volumes of AA) are recommended for younger pediatric patients, a vial with a large quantity of excess drug may pose an even greater risk of overdosing in pediatric patients. In addition, pediatric patients less than 2 years of age may be at greater risk of adverse consequences related to over dosing secondary to their renal immaturity.

A safe level of pediatric exposure to EDTA has not been identified; however, hypotension and hypocalcemia have been identified with high exposures of EDTA. The AA and EDTA content of the proposed single-use vial must be addressed to assure safe use of this product in pediatric patients.

If (b) (4) is approved as a Pharmacy Bulk Package and, as such, overdosing errors are highly unlikely, DPMH is not concerned about the risk of AA or EDTA overdose in pediatric patients being treated for scurvy and labeling is not needed to warn of these risks. However, the availability of a vial with a high volume of excess drug product may contribute to off-label use.

D. Recommendations

1. DPMH recommends labeling (b) (4) for use in pediatric patients five months of age and older.
2. Given the limited available data, DPMH suggests the following pediatric dosing cohorts:
 - Pediatric patients 11 years and older: 200 mg/day
 - Pediatric patients 1 year to < 11 years: 100 mg/day

⁴⁶ FDA Guidance for Industry. "Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products". June 2015.

- Pediatric patients 5 months to < 1 year: 50 mg/day
3. Repeat dosing in pediatric patients 11 years and older is acceptable. Repeat dosing (b) (4) is not recommended. (b) (4)
(b) (4)
(b) (4)
 4. DMEP may wish to consider not only providing the mg dose in labeling, but also the dose in mL to help prevent dosing errors.
 5. If (b) (4) is approved as a single-use vial, DMEP should consider the risk of toxicity associated with over dosing of both AA (especially in patients less than two years whose renal function is not mature) and the excipients (particularly EDTA).
 6. If (b) (4) is approved as Pharmacy Bulk Product, and as such dosing errors are considered highly unlikely, DPMH does not recommend labeling for the risks of toxicity related to overdosing.
 7. DPMH suggests further discussion with DMEPA to determine the approvability of this product as a 50 mL vial. DMEP should consider whether the large volume per vial will contribute to off-label use.
 8. Labeling
 - a. Given that the terms (b) (4) and (b) (4) may be misinterpreted as referring to healthy individuals of unspecified age and this product is being labeled for patients five months and older with scurvy, replace the terms (b) (4) and (b) (4) with “pediatric patients” throughout labeling.
 - b. Given that the available data suggest that orally administered AA is bioavailable and effective in the treatment of scurvy and that the available safety and efficacy data for the treatment of pediatric patients with scurvy is based on oral administration of AA, retain labeling language which states that IV AA should be used short-term and/or when oral administration is not clinically appropriate.
 - c. Modify the age cohorts throughout labeling to ensure that overlap and gaps in dosing recommendations do not exist.

- d. Consider providing information in labeling about assessing the severity of clinical disease to aid prescribers in dose selection or consider removing [REDACTED] (b) (4)
[REDACTED]
- e. Remove [REDACTED] (b) (4)
[REDACTED] as per the version of labeling available on September 8, 2017.
- f. Add the following sentence to section 5.1:
“Pediatric patients less than two years of age may be at higher risk of oxalate nephropathy following ascorbic acid administration because of their renal immaturity. [see Subsection 8.4 (Pediatric Use)].”
- g. Entitle Subsection 8.4 “Pediatric Use”. DPMH recommends the following language for subsection 8.4:

ASCOR is indicated for the short term (up to 1 week) treatment of scurvy in pediatric patients age 5 months and older for whom oral administration is not possible, insufficient or contraindicated.” The safety profile of ascorbic acid in pediatric patients is similar to adults; however, pediatric patients less than 2 years of age may be at higher risk of oxalate nephropathy following ascorbic acid administration due to age-related decreased glomerular filtration [see Warnings and Precautions (5.1)].

Ascor is not indicated for use in pediatric patients less than 5 months of age.

- h. Unless the applicant provides supporting data, remove the following statement from 8.4: [REDACTED] (b) (4)

[REDACTED]
[REDACTED]

DPMH shared these labeling recommendations with DMEP on September 6, 2017 and September 19, 2017.

Appendix A: Vitamin C Requirements

Patient Population			IV AA Proposed Daily Dosing (b) (4)	Vitamin C RDA ^a (oral)	Vitamin C UIL ^a (oral)	Multivitamin infusions (adult) ^b	Multivitamin infusions (pediatric) ^c	ASPEN Guidelines ^d (daily requirements)		
Adults (≥ 18 years)	Male		(b) (4)	90 mg	2000 mg	200 mg	NL ^a	90 mg (oral) 100 mg (IV)		
	Female			75 mg	2000 mg					
Pediatrics	14-18 years	Male		75 mg	1800 mg			NL	“Infants and Children < 11 years) > 3 kg = 80 mg 1-< 3 kg = 52 mg < 1 kg = 24 mg	N/A
		Female		65 mg	1800 mg					
	11-13 years			45 mg	1200 mg					
	9-10 years			25 mg	650 mg					
	4- 8 years			15 mg	400 mg					
	1-3 years			AI ^m from human milk: 50 mg (~ 6 mg/kg)						
	≥ 6 months – 12 months									
	0-6 months			AI ^m from human milk: 40 mg (~ 6 mg/kg)						
Special Populations	Pregnant women ≥ 18 years			85 mg	2000 mg	Labeling states follow RDA ^a .	NL	N/A		
	Breast feeding women ≥ 18 years			120 mg	2000 mg	Labeling states “caution should be exercised”.	NL			
	Pregnant 14-18 years			80 mg	1800 mg	No specific labeling for this age group.	NL. Infivite labeling states follow RDA.			
	Breast feeding 14-18 years			115 mg			NL. Labeling states “caution should be exercised”.			
	Renal impairment			N/A	N/A	Labeling states monitor renal function, calcium, phosphorus and vitamin A levels				
	G6PD* deficiency			N/A	N/A	No information in labeling	No information in labeling			
^a Abbreviations Used AI: Average Intake. The AI for children birth to 12 months is based on the average volume of milk intake. G6PD: Glucose-6 Phosphate Dehydrogenase										

IV: Intravenous

N/A: Not available or Not identified

ND: Not determinable due to lack of data on the adverse effects of vitamin C in this age group and concern regarding the ability of children to excrete excess amounts of vitamin C. Sources of vitamin C intake should be from food only to prevent high levels of intake.

NL: Not labeled for this age group

NTE: Not to Exceed

RDA: Recommended Daily Allowance is the average daily dietary intake level; sufficient to meet the nutrient requirements of nearly all (97-98 percent) healthy individuals in a group. RDAs in adults are based on neutrophil concentration and urinary excretion. RDAs in children are estimated based on body weight (Data from: Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. National Academies Press, Washington, DC, 2000)

UIL: Tolerable Upper Intake Level is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population. (Data from: Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. National Academies Press, Washington, DC, 2000)

^b M.V.I.-Adult™ (NDAs 021625 & 021643) and Infuvite Adult (NDAs 021163 & 021559), multiple vitamins for injection products, are approved for the prevention of vitamin deficiency in adults and pediatric patients 11 years and older receiving parenteral nutrition. Vitamin C dosing is 200 mg per day.

^c M.V.I. Pediatric® (NDA 018920) and Infuvite Pediatric (NDAs 021265 & 021646), multiple vitamins for injection products, are approved for maintenance dosage and prevention of vitamin deficiency, respectively, in pediatric patients up to 11 years receiving parenteral nutrition. Dosing is weight based. Data on which the pediatric dosing regimen was determined is not provided in product labeling. No other pediatric parenteral nutrition formulations identified.

^d ASPEN Guidelines provide daily AA requirements for “infants and children < 11 years” and “adults”. The guidelines do not provide the data or strength of the data to support the doses recommended and per the guidelines, should be considered approximations of need. ASPEN Board of Directors and the Clinical Guidelines Task Force. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. *J Parenter Enteral Nutr.* 2002;26(1 Suppl):1SA–138SA ([link](#))

Appendix B: Vitamin C Dose Range Recommendations for Parenteral Nutrition⁴⁷

Copyright material



⁴⁷ Berger MM. Vitamin C Requirements in Parenteral Nutrition. *Gastroenterology*. 2009;137:S70-S78.

Appendix C: Ascorbic Acid Dosing for the Treatment of Scurvy

Note: Although the applicant proposes dosing (i.e., not to exceed the Recommended Daily Allowance or (b) (4)) for special populations (i.e. (b) (4), glucose-6-phosphate dehydrogenase deficiency, women who are pregnant or nursing), the sources (b) (4) patients for the treatment of scurvy.

Source	Description of Source	Daily Dosing		Dosage Form/Route of Administration	Data/Citations to Support Dosing	Safety/Toxicity	Comments
		Pediatric	Adult				
IV AA* Proposed Daily Dosing ((b) (4))	Applicant's proposed dosing regimen (b) (4)	(b) (4)		IV*	One phase 1 pharmacokinetic (PK), safety and tolerability study in healthy adults and information from the published literature	Information in labeling	(b) (4)
Harriet Lane Handbook ⁴⁸	Pediatric Dosing Guidelines for Clinicians	"Child" 100-300 mg/24 hours divided daily or twice daily for a minimum of 2 weeks.	Adult: 100-250 mg daily or twice daily for at least 2 weeks	Oral, IV, IM*, SC* "Oral dosing is preferred. IM route is the preferred parenteral route."	Not provided	Adverse reactions: nausea, vomiting, heartburn, flushing, headache, faintness, dizziness, hyperoxaluria.	—
Up to Date ⁴⁹	Evidence-based, physician-authored clinical	"Children": 100 mg AA 3 times daily x 1 week,	"Adults are usually treated with 300 to	Not specified	AAP* Nutrition Handbook (2011) ⁵⁰	"A number of side effects of ascorbic acid have been reported in the literature." ⁵¹	"a wide range of replacement doses have been used successfully"

⁴⁸ Custer JW, Rau RE. eds. *The Harriet Lane Handbook*. 18th ed. Philadelphia, PA: Elsevier Mosby; 2009. 738.

⁴⁹ Up to Date. <https://www.uptodate.com/contents/overview-of-water-soluble-vitamins?source=machineLearning&search=scurvy&selectedTitle=1~48§ionRank=1&anchor=H54#H54> Accessed August 30, 2017.

⁵⁰ Up to Date reported citation: American Academy of Pediatrics. Water-soluble vitamins. In: Pediatric Nutrition, 7th ed., Kleinman RE, Greer FR (Eds), American Academy of Pediatrics, Elk Grove Village 2011. p.527. DPMH was not able to obtain a copy of this resource at the time of finalization of this review. *Not available for review.*

⁵¹ Although some additional information provided in the table following this statement is provided, limited additional information is reported about side effects.

Source	Description of Source	Daily Dosing		Dosage Form/Route of Administration	Data/Citations to Support Dosing	Safety/Toxicity	Comments
		Pediatric	Adult				
	decision support resource	then once daily for several weeks until full recovery.	1000 mg daily for one month”		Weinstein (2001) Hirschmann (1999)	Large doses of vitamin C (in gram quantities) ... have been associated with diarrhea and abdominal bloating. High-dose vitamin C therapy may also increase oxalate formation and the risk for calcium oxalate kidney stones. Ingestion of large quantities of ascorbic acid has been rarely associated with fatal cardiac arrhythmias in patients with iron overload, presumably due to oxidative injury.	
Micromedix ⁵²	Evidence-based resource for clinical decision making	Oral, IM or IV: Adults and children 100 mg 3X a day for 2 week, then 200 mg per day for several weeks. The maximum recommended IV dose for AA in patients 17 years and younger is 100 mg/kg/day up to 6 gram/day	Oral, IM or IV: Adults and children 100 mg 3X a day for 2 week, then 200 mg per day for several weeks	Oral, IM, IV	AMA*: AMA Drug Evaluations Subscription, vol 2. American Medical Association, USA, 1990, 1990 Oeffinger KC: Scurvy: more than historical relevance. Am Fam Phys 1993; 48:609-613. <i>Ordered</i> Anon: Guidelines for Administration of Intravenous	No specific pediatric safety concerns identified.	Two different recommendations are provided in the adult dosing section. The adult dosing section recommends 200 to 500 mg/day oral, IM or IV for treatment of severe burns. Micromedex states that AA deficiency is a labeled FDA indication in pediatric and adult patients.

⁵² Micromedix Solutions® 2.0, (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: <http://www.micromedixsolutions.com/direct-link> (Accessed August 29, 2017).

Source	Description of Source	Daily Dosing		Dosage Form/Route of Administration	Data/Citations to Support Dosing	Safety/Toxicity	Comments
		Pediatric	Adult				
		No additional recommendations	1 to 2 grams IV or oral for the first 2 days then 500 mg IV or oral daily for a week				
					Medications to Pediatric Patients, 2nd. American Society of Hospital Pharmacists, Bethesda, MD, 1984a. Recommendation Rating ^a : Class I for adult and pediatric patients. Strength of the evidence for [dosing recommendations] pediatric and adult patients ^b : Category B		
Weinstein⁵³	Case report (n=1) and review article. Cited by Up to Date [®]	“Infants and children are usually treated with 100 to 300 mg daily”	“Adults 500 to 1000 mg daily”	Not specified	Baumbach (1994) Ellis (1984) Friedman (1965) Reuler (1985)	Not discussed	N=1 treated with 250 mg/day; Clinical signs and symptoms improved within one week. Recommended duration of treatment: “1 month or until full recovery occurs”
Hirschmann⁵⁴	Review article	Not discussed	“a dose that both corrects the deficit and	Not specified	Three citations (n= 2 published in	Not discussed	N=1 treated with 500 mg/day administered 2x daily.

⁵³ Weinstein M, Babyn P, Zlotkin, S. An orange a day keeps the doctor away: scurvy in the year 2000. *Pediatrics*. 2001;108(3):e55-e55.

⁵⁴ Hirschmann JV, Raugi GJ. Adult Scurvy. *Journal of the American Academy of Dermatology*. 1999;41(6):895-910 ([link](#)).

Source	Description of Source	Daily Dosing		Dosage Form/Route of Administration	Data/Citations to Support Dosing	Safety/Toxicity	Comments
		Pediatric	Adult				
	Cited by Up to Date®		repletes the body stores expeditiously is 100 mg 3 times a day”		1946, n=1 published in 1958)		
Baumbach ⁵⁵	Case report Cited by Weinstein	“Recommendations for treatment of scurvy range from daily doses of 10-100 mg vitamin C in mild disease to 500 – 1000 mg in severe disease”		Not specified	No citation provided	Not discussed	–
Ellis ⁵⁶	Case report and review Cited by Weinstein	Patient treated with 250 mg daily “infants and children: 150-300 mg/day orally for one month”	“as much as 800 mg/day in divided doses for one week and 400 mg/day until complete recovery”	Oral	McLaren DS: Cutaneous changes in nutritional deficiencies, in Fitzpatrick TB, Eisen AZ, Wolff K, et al (eds): Dermatology in General Medicine, ed 2. New York, McGraw-Hill Book Co Inc, 1979, pp 1029-1030. ⁵⁷	Not discussed	–
Friedman	Scientific paper Cited by Weinstein	Not provided	Not provided	–	–	–	–
Reuler ⁵⁸	Case reports (n=3) and review	Not provided	“300 mg/day will replenish body stores”	Not specified	Not provided	Not discussed	–

⁵⁵ Baumbach J. Scurvy by another name: a case report. *RI Med*. 1994;77: 24–25.

⁵⁶ Ellis CN, Vanderveen EE, Rasmussen JE. Scurvy: a case caused by peculiar dietary habits. *Arch Dermatol*. 1984;120:1212–1214.

⁵⁷ Citation for recommended dosing: McLaren DS: Cutaneous changes in nutritional deficiencies, in Fitzpatrick TB, Eisen AZ, Wolff K, et al (eds): Dermatology in General Medicine, ed 2. New York, McGraw-Hill Book Co Inc, 1979, pp 1029-1030. *DPMH did not pursue obtaining this reference.*

⁵⁸ Reuler JB, Broudy VC, Cooney TG. Adult scurvy. *JAMA*. 1985;253: 805–807 ([link](#)).

Source	Description of Source	Daily Dosing		Dosage Form/Route of Administration	Data/Citations to Support Dosing	Safety/Toxicity	Comments
		Pediatric	Adult				
	Cited by Weinstein						
Ratanachu-ek⁵⁹	Retrospective chart review (n=28)1995-2002	Reports treatment with 150-300 mg/day (duration of treatment not reported)	Not discussed	Not specified (presumed oral)	Not provided	Not discussed	All patients gradual improvement in days
Oeffinger⁶⁰	Review article	Not provided	Standard Treatment: 1 to 2 gram IV for two days, followed by 500 mg daily (route not specified) for one week.	IV, (likely Oral)	Not provided	Not discussed	—
Grewar⁶¹	Review article (including a case report)	100-1000 mg daily	Not specifically discussed	Oral, IM	Not provided	Not discussed	Author states “no practical advantage of larger doses of the vitamin” and 2 to 4 ounces of fresh orange juice results in equally prompt relief of symptoms.
Mayo Clinic Web site⁶²	Evidence-based monograph by The Natural Standard	“100-300 mg of AA has been taken by mouth daily in divided	“100-250 mg of AA was given by mouth four times daily for one week.”	Oral or injection	“based on scientific research, publications, traditional use, or expert opinion”	“Vitamin C is generally regarded as safe in amounts normally obtained from foods. Vitamin C supplements are also	Dosing also provided for other effects and conditions including antioxidant effects, cancer prevention,

⁵⁹ Ratanachu-Ek S, Sukswai P, Jeerathanyasakun Y, Wongtapradit, L. Scurvy in pediatric patients: a review of 28 cases. *Journal of the Medical Association of Thailand*. 2003;86,:S734 ([link](#)).

⁶⁰ Oeffinger KC. Scurvy: More Than Historical Relevance. *American Family Physician*. 1993;48(4):609-13.

⁶¹ Grewar D. Infantile Scurvy. *Nutrition*. 1965;4(2):82-89.

⁶² Vitamin C. Drugs & Supplements. Patient Care & Health info Mayo Clinic Web site available @ <http://www.mayoclinic.org/drugs-supplements/vitamin-c/dosing/HRB-20060322>. Accessed August 30, 2017.

Source	Description of Source	Daily Dosing		Dosage Form/Route of Administration	Data/Citations to Support Dosing	Safety/Toxicity	Comments
		Pediatric	Adult				
	Research Collaboration	doses for two weeks.” “Older or larger children may require doses closer to adult recommendations” “If vitamin C is unavailable, orange juice may	“Some experts have recommended 1-2 grams daily for two days, followed by 500 mg daily for one week”		No references provided regarding AA dosing for scurvy.	generally regarded as safe in most individuals in recommended amounts.”	prevention and treatment of the common cold, prevention of complex regional pain syndrome, fertility, heart conditions, H. pylori infection, kidney disease, liver disease and “full life extension”.

(b) (4)

(b)
)
(4

Source	Description of Source	Daily Dosing		Dosage Form/Route of Administration	Data/Citations to Support Dosing	Safety/Toxicity	Comments
		Pediatric	Adult				
(b) (4)							
Approved AA Product in Germany	Pascorbin ⁶⁴	Oral, IM, IV, SC: 100 to 300 mg/day in divided doses for a minimum of two weeks.	Oral, IM, IV, SC: 100 to 250 mg once or twice daily for a minimum of two weeks.	Oral, IM, IV, SC	Not provided	No pediatric specific safety warnings	The applicant provided different Pascorbin labeling than the labeling identified by DPMH (see the Summary of Clinical Efficacy; Original NDA; Section 2.7.3, Table 14).
*Abbreviations Used in Table: AA: Ascorbic Acid AAP: American Academy of Pediatrics AMA: American Medical Association IM: Intramuscular IV: Intravenous NTE: Not to Exceed PK: Pharmacokinetics RDA: Recommended Daily Allowance SC: Subcutaneous							
^a Class 1: Recommended - The given test or treatment has been proven to be useful, and should be performed or administered. ^b Category B evidence is based on data derived from (1) meta-analyses of randomized controlled trials with conflicting conclusions with regard to the directions and degrees of results between individual studies, (2) randomized controlled trials that involved small numbers of patients or had significant methodological flaws (e.g., bias, drop-out rate, flawed analysis, etc.) or (3) nonrandomized studies (e.g., cohort studies, case-control studies, observational studies).							

⁶⁴ Pascorbin ;labeling information identified on nDrugs web site available @ <http://www.ndrugs.com/?s=pascorbin&t=dosage>. Accessed August 31, 2017.

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/s/

ELIZABETH L DURMOWICZ

09/19/2017

MONA K KHURANA

09/19/2017

Mona Khurana signing on behalf of John J. Alexander, Deputy Director for the Division of Pediatric and Maternal Health

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: August 22, 2017

To: Abolade Adeolu, Regulatory Project Manager
Division of Metabolism & Endocrine Products (DMEP)

From: Charuni Shah, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 209112
OPDP labeling comments for ASCORBIC ACID INJECTION, for intravenous use.

On September 6, 2016, OPDP received a consult request from DMEP to review proposed Prescribing Information (PI) and carton/container labeling for ASCORBIC ACID INJECTION, for intravenous use

OPDP's review of the draft labeling is based on the version sent via e-mail by Abolade Adeolu on August 21, 2017. OPDP's comments are reflected in the attached version of the labeling.

OPDP does not have any comments on the carton/container labeling at this time.

Thank you for the opportunity to comment on this material.

If you have any questions, please contact Charuni Shah at 240-402-4997 or Charuni.Shah@fda.hhs.gov.

14 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

CHARUNI P SHAH
08/22/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 15, 2017
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 209112
Product Name and Strength:	Ascor (ascorbic acid injection, USP) 25 g/50 mL (500 mg/mL)
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	McGuff Pharmaceuticals, Inc.
Submission Date:	September 2, 2016 and December 14, 2016
OSE RCM #:	2016-2070
DMEPA Primary Reviewer:	Sarah K. Vee, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

Division of Metabolism and Endocrinology Products (DMEP) requested that we review the proposed labels and labeling submitted under NDA 209112 on September 2, 2016 for ascorbic acid injection as part of the 505(b)(2) submission.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	N/A
Human Factors Study	N/A
ISMP Newsletters	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	N/A
Labels and Labeling	B

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

McGuff Pharmaceuticals, Inc. submitted NDA 209112 for ascorbic acid injection. We performed a risk assessment of the proposed container label and carton labeling and prescribing information to identify deficiencies that may lead to medication errors and other areas of improvement. DMEPA identified areas in the container label and carton labeling that can be improved to relay important information and promote the safe use of the product. We recommend the following enhancements or changes to mitigate any confusion: relocation of important information from the side panel to the principal display panel and the prominence of established name.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information and promote the safe use of the product and mitigate any confusion.

4.1 RECOMMENDATIONS FOR MCGUFF PHARMACEUTICALS

We recommend the following be implemented prior to approval of this NDA:

- A. Container Label

1. Revise the statement “Pharmacy Bulk Package: (b) (4)” to “Must dilute before use” on the principal display panel to minimize the risk of the product being administered without dilution.
 2. Add the statement “Single-Dose Vial – Discard Unused Portion” to minimize risk of the entire contents of the vial being given as a single dose.^a
 3. Relocate the route of administration statement, “For Intravenous Use Only”, from the side panel to the principal display panel.
 4. The established name is not at least half the size of the proprietary name and the established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
 5. The container label of (b) (4) and the carton labeling of (b) (4) should have different NDC numbers. Revise the NDC numbers so that the carton labeling and vial label NDC numbers are different for these two package configurations.
- B. Carton Labeling
1. See A.1., A.2, A.3, and A5.
 2. Add the proprietary name and ensure that same recommendations are applied as A.4.
 3. Relocate the “Rx Only” statement away from the route of administration statement.

^a Draft Guidance: Appropriate Package Type Terms, October 2015 (lines 91-93)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ascor that McGuff Pharmaceuticals submitted on September 2, 2016 and December 14, 2016.

Table 2. Relevant Product Information for Ascor	
Initial Approval Date	N/A
Active Ingredient	Ascorbic acid
Indication	For the treatment of scurvy
Route of Administration	Intravenous infusion
Dosage Form	Injection
Strength	500 mg/mL (25 g/50 mL)

Dose and Frequency	(b) (4)
How Supplied	Tray of 25, 50 mL, pharmacy bulk (b) (4)
Storage	Store in refrigerator at 2° to 8°C (36° to 46°F). (b) (4) (b) (4)
Container Closure	50 mL Glass vial packaged in chipboard tray carton

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

/s/

SARAH K VEE
03/15/2017

HINA S MEHTA
03/16/2017

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 209112	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Ascor (pending) Established/Proper Name: submitted as "ascorbic acid" however per CMC established name should be "sodium ascorbate" Dosage Form: injection Strengths: 500 mg/mL		
Applicant: McGuff Pharmaceuticals, Inc. Agent for Applicant (if applicable):		
Date of Application: 8.31.2016 Date of Receipt: 9.2.2016 Date clock started after Unacceptable for Filing (UN):		
PDUFA Goal Date: 7.2.2017		Action Goal Date (if different):
Filing Date: 11.1.2016		Date of Filing Meeting: 10.13.2016
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☒ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): Treatment of scurvy		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
<i>If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		

Type of BLA <i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>		☐ 351(a) ☐ 351(k)		
Review Classification: <i>The application will be a priority review if:</i> - A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH) - The product is a Qualified Infectious Disease Product (QIDP) - A Tropical Disease Priority Review Voucher was submitted - A Pediatric Rare Disease Priority Review Voucher was submitted		☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher		
Resubmission after withdrawal? ☐		Resubmission after refuse to file? ☐		
Part 3 Combination Product? ☐ <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)			
☐ Fast Track Designation ☐ Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other: Orphan designation # 07-3437 granted for tx of scurvy on 8/31/2007	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 076483				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in the electronic archive?	☒	☐		
<i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>				
Are the established/proper and applicant names correct in electronic archive?	☒	☐		Established name submitted by applicant as "ascorbic

<i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.</i>				acid" but should be "sodium ascorbate" per CMC. Name updated in DARRTS [JV1].
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	☒	☐	☐	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	☐	☒		
<i>If yes, explain in comment column.</i>				
If affected by AIP, has OC been notified of the submission? If yes, date notified:	☐	☐		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		Form 3397
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment for this application (check daily email from UserFeeAR@fda.hhs.gov): ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment of other user fees: ☒ Not in arrears ☐ In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> ☒ Yes ☐ No			

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment																
Is the application a 505(b)(2) NDA? (Check the 356h form, cover letter, and annotated labeling). If yes, answer the bulleted questions below:	☒	☐																		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒																		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].	☐	☒																		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?	☐	☒																		
<i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>																				
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm	☐	☒																		
If yes, please list below: <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>					Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration												
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>																				
Exclusivity	YES	NO	NA	Comment																
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm	☐	☒																		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	☐	☐	☒																	
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>																				
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	☒	☐	☐	(b) (4)																

If yes, # years requested (b) (4)				
<i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?	☐	☐	☐	
<i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>				
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?	☐	☐	☐	
<i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i>				
<i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21	☒	☐		

¹ <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>

CFR 601.2 (BLAs/BLA efficacy supplements) including: ☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	☐	☐	☐	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included.</i> Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	☒	☐		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☐	☒	☐	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	☒	☐		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	☐	☐	X	
<i>If yes, ensure that the application is also coded with the</i>				

supporting document category, "Form 3674."				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	☒	☐	☐	
<i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>				
<i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?	☐	☐	☒	
<i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i>				
<i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>				
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?	☐	☐	☒	
<i>If yes, date consult sent to the Controlled Substance Staff:</i>				
<u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>				
Pediatrics	YES	NO	NA	Comment

<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	☐	☒		Orphan designation
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	☐	☐	☒	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	☐	☐	☒	
<u>BPCA:</u> Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required³</i>	☐	☒		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	☒	☐	☐	Ascor- approved conditionally under IND 076483(6/23/2016)
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	☐	☒	☐	
Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide)			

2

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm>

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm>

	☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	☒	☐		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in Physician Labeling Rule (PLR) format? ⁴	☒	☐		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format?	☐	☒	☐	Request in 74-day letter
Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☐	☒	☐	Request in 74-day letter
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.</i>	☐	☒	☐	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (send WORD version if available)	☐	☐	☒	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ Not Applicable			

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm>

Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	☐	☐		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	☐	☐	☐	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	☐	☐	☐	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	☒	☐	☐	DPMH-9/12/2016
<i>If yes, specify consult(s) and date(s) sent: DPMH-9/12/2016</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): WRO-9/22/2011	☒	☐		Pre-NDA meeting WRO -9/22/2011
Any Special Protocol Assessments (SPAs)? Date(s):	☐	X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 10/13/2016

BACKGROUND:

McGuff Pharmaceuticals, Inc, submitted on September 2, 2016, a new drug application (NDA) for ascorbic acid for injection. This is a 505(b)(2) NDA relying on published literature. This is also an NDA type 7-drug already marketed without an approved NDA.

On August 31, 2007, orphan drug designation was granted for ascorbic acid for the treatment of scurvy (Designation #007-2437).

Proprietary name Ascor was conditionally approved under IND 076483 on June 23, 2016. PDUFA goal date for this application is July 2, 2017.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Abolade (Bola) Adeolu	Y
	CPMS/TL:	Julie Van der Waag	Y
Cross-Discipline Team Leader (CDTL)	Marina Zemskova		Y
Division Director/Deputy	Jean-Marc Guettier		N (Jennifer Pippins, DDS was covering)
Office Director/Deputy			
Clinical	Reviewer:	William Lubas	Y
	TL:	Marina Zemskova	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Dipak Pisal	Y
	TL:	Jaya Vaidyanathan	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:		
	TL:		

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Parvaneh Espandiari	Y
	TL:	Calvin (Lee) Elmore	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Suong Tran	Y
	RBPM:	Anika Lalmansingh	Y
• Drug Substance	Reviewer:	Sukhamaya (Sam) Bain	N
• Drug Product	Reviewer:	Muthu Ramaswamy	N
• Process	Reviewer:	Hong Yang	N
• Microbiology	Reviewer:	TBD	N
• Facility	Reviewer:	Michael (Mike) Klapal	N
• Biopharmaceutics	Reviewer:		
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Charuni Shah	N
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Sarah Vee	N
	TL:	Hina Mehta	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• DPMH	Reviewer:	Carol Kasten	Y
	TL:	Tamara Johnson	Y
Other attendees	Sally Loewke		Y
	Denise Pica-Branco		Y
	Anika Lalmansingh		Y
	Shannon Sullivan		Y
	Larry Bauer		Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☐ Not Applicable ☐ YES ☒ NO ☒ YES ☐ NO Applicant conducted a pharmacokinetic study
• Per reviewers, are all parts in English or English translation? If no, explain:	☒ YES ☐ NO
• Electronic Submission comments	☐ Not Applicable ☒ No comments

List comments:	
CLINICAL	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE
Comments:	☐ Review issues for 74-day letter
Clinical study site(s) inspections(s) needed? If no, explain:	☐ YES ☒ NO
- Advisory Committee Meeting needed? Comments: <i>If no, for an NME NDA or original BLA, include the reason. For example:</i> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE
Abuse Liability/Potential Comments:	☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE
Comments:	☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity (NDAs only)</u> Is the product an NME?	☐ YES ☒ NO
<u>Environmental Assessment</u> Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? Comments:	☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> Establishment(s) ready for inspection? Comments:	☐ Not Applicable ☒ YES ☐ NO

<u>Facility/Microbiology Review (BLAs only)</u> Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review (BLAs only)</u> Comments:	☐ Review issues for 74-day letter
<u>APPLICATIONS IN THE PROGRAM (PDUFA V)</u> <u>(NME NDAs/Original BLAs)</u> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Jean-Marc Guettier, MD Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Mid-cycle meeting: 2/2/2017 Wrap Up meeting: 5/25/2017 Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. <u>Review Classification:</u> ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAAs completed: April 2016

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

/s/

ABOLADE ADEOLU
10/31/2016

REGULATORY PROJECT MANAGER PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 209112

Application Type: New NDA (Type 7)

Drug Name(s)/Dosage Form(s): ascorbic acid injection

Applicant: McGuff Pharmaceuticals

Receipt Date: September 2, 2016

Goal Date: July 2, 2017

1. Regulatory History and Applicant's Main Proposals

McGuff Pharmaceuticals, Inc, submitted on September 2, 2016, a new drug application (NDA) for ascorbic acid for injection. This is a 505(b)(2) NDA relying on published literature. This is also an NDA type 7-drug already marketed without an approved NDA.

On August 31, 2007, orphan drug designation was granted for ascorbic acid for the treatment of scurvy (Designation #007-2437).

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

In addition, the following labeling issues were identified:

Remove heading (b) (4) appears above "Highlights of Prescribing Information"

Length of HL is greater than one-half page

No horizontal line between TOC and FPI

There is white space between HL Heading and HL limitation statement. There should be white space between HL limitation statement and Product title.

Name of drug not consistent in the Highlights limitation statement.

Line on either side of FULL PRESCRIBING INFORMATION label needs to be deleted

Selected Requirements of Prescribing Information

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.
- Comment:**
- NO** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.
- Comment:** *Length of HL is greater than one-half page*
- NO** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).
- Comment:** *No horizontal line between TOC and FPI*
- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.
- Comment:**
- NO** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.
- Comment:** *There is white space between HL Heading and HL limitation statement. There is white space between Product title and Initial US approval.*
- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.
- Comment:**
- NO** 7. Headings in HL must be presented in the following order:

Selected Requirements of Prescribing Information

Heading	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading, "**HIGHLIGHTS OF PRESCRIBING INFORMATION**" must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

- NO** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment: Name of drug not consistent.

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

Selected Requirements of Prescribing Information

- N/A** 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term “**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “*See full prescribing information for complete boxed warning.*”)

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

Comment:

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Selected Requirements of Prescribing Information

Contraindications in Highlights

- YES** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

Comment:

Adverse Reactions in Highlights

- YES** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

Comment:

Patient Counseling Information Statement in Highlights

- YES** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

- NO** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015** ”).

Comment: *At the bottom of page*

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

- YES** 24. The TOC should be in a two-column format.
Comment:
- YES** 25. The following heading must appear at the beginning of the TOC: **“FULL PRESCRIBING INFORMATION: CONTENTS.”** This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].
Comment:
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading **“FULL PRESCRIBING INFORMATION: CONTENTS*”** must be followed by an asterisk and the following statement must appear at the end of the TOC: **“*Sections or subsections omitted from the full prescribing information are not listed.”**
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

NO

31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: 8. Use in Specific Population is not in PLLR format

NO

32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "[see *Warnings and Precautions (5.2)*]."

Comment: No cross-references used in FPI

Selected Requirements of Prescribing Information

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- NO** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment: *Line on either side needs to be deleted*

BOXED WARNING Section in the FPI

- N/A** 35. All text in the BW should be **bolded**.

Comment:

- N/A** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- N/A** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

N/A 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

N/A 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PROPRIETARY NAME** safely and effectively. See full prescribing information for **PROPRIETARY NAME**.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

CONTRAINDICATIONS

- Text (4)
- Text (4)

WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report **SUSPECTED ADVERSE REACTIONS**, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling **OR** and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

ABOLADE ADEOLU
10/31/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of the Commissioner
Office of Good Clinical Practice
10903 New Hampshire Avenue, Bldg. 32, Rm. 5110
Silver Spring, MD 20993-0002
Telephone: 301-796-3707

MEMORANDUM

Date: October 27, 2016

From: Kevin Prohaska, D.O., M.P.H., Captain (USPHS)
Office of Good Clinical Practice, Office of the Commissioner

Through: Joanne Less, Ph.D., Director
Office of Good Clinical Practice, Office of the Commissioner

To: William Lubas, M.D., Medical Officer
Division of Metabolism & Endocrinology Products, CDER

Re: NDA 209112: Ascorbic Acid for the Treatment of Scurvy

I. Materials Reviewed

- 1) Council for International Organizations of Medical Sciences (CIOMS), "International Ethical Guidelines for Biomedical Research Involving Human Subjects":
<http://www.recerca.uab.es/ceeah/docs/CIOMS.pdf>
- 2) Emanuel EJ, et al, "What Makes clinical Research Ethical?", JAMA May 24/31, 2000: 2701-11
- 3) Hodges RE., et. al., "Experimental Scurvy in Man", American Journal of Clinical Nutrition: vol. 22, May 1969, 535-548
- 4) Hodges, RE., et. al., "Clinical Manifestations of Ascorbic Acid Deficiency in Man", American Journal of Clinical Nutrition: vol. 24, April 1971, 432-443
- 5) Krebs HA, et. al., "The Sheffield Experiment on the Vitamin C Requirements of Human Adults", Lind Bicentenary Symposium, Proceedings from Nutrition Society, vol. 12, September 1953, 237-246
- 6) Nuremberg Code, available at
<https://history.nih.gov/research/downloads/nuremberg.pdf>
- 7) Declaration of Helsinki 1964, available at <http://hämovigilanz.eu/en/helsinki64.html>
- 8) Hirschmann, JV et. al., "Adult Scurvy", Journal of Academic Dermatology, December 1999, 895-906
- 9) Pemberton, J, "Medical Experiments Carried out in Sheffield on Conscientious Objectors to Military Service During the 1939-45 War", International Journal of Epidemiology, January 2006; 35: 556-558
- 10) World Health Organization report "Scurvy and its Prevention and Control in Major Emergencies", available at
http://www.who.int/nutrition/publications/emergencies/WHO_NHD_99.11/en/

- 11) Bateman-House A, “Men of Peace and the Search for the Perfect Pesticide: Conscientious Objectors, the Rockefeller Foundation, and the Typhus Control Research”, Public Health Reports, July-August 2009, vol 124, 594-602.
- 12) Clark RA, et. al., “The Work of Conscientious Objectors in State Mental Hospitals During the Second World War”, Psychiatric Quarterly, Supplement, 1948; 22, 128-40
- 13) Coughlin SS, et. al., “Ethical and Social Issues in Health Research Involving Incarcerated People”, Journal of Health Care for the Poor and Underserved, 2016, 27 18-28
- 14) Gostin LO, et. a;., “Ethical Consideration for Research Involving Prisoners”, National Academy Press 2007
- 15) Response to Information Request dated October 24, 2016
- 16) Hodges RE et. al., “The Use of Prisoners for Medical Research”, JAMA, Nov 6, 1967, Vol 202, No 6, 177-179

II. Background

On October 13, 2016 the Office of Good Clinical Practice (OGCP) within the Office of Medical Products and Tobacco received a consultative request from the Division of Metabolism & Endocrinology Products in the Center for Drug Evaluations and Research (CDER). The purpose of the request is for an OGCP ethical consultation to address the following concerns related to NDA 209112:

McGuff Pharmaceutical submitted a NDA for ascorbic acid for the treatment of scurvy in adults and children. This is a 505 (b)(2) application relying on the data derived from the published literature. Two published studies (Hodges et al. 1969 and 1971) evaluated use of vitamin C in prisoners who were given diets low in vitamin C in order to induce scurvy. Please, determine if these studies will be acceptable as support for approval of a product, given the controversies surrounding the issue of whether prisoners can truly give informed consent for medical research. In addition, one article (Krebs 1953) included healthy volunteers who considered themselves pacifists and were relieved of their required military service obligations in WWII by volunteering for a similar study in which they developed scurvy by eating a diet deficient in vitamin C. Please determine if it is acceptable to use these data as well to support approval of ascorbic acid for the treatment of scurvy.

Scurvy is a disease long known to be caused by a deficiency of vitamin C (ascorbic acid). Early symptoms of scurvy are nonspecific and include generalized lethargy, myalgia, and arthralgia. Later signs and symptoms include skin (hyperkeratosis, perifollicular hemorrhage, ecchymosis, xerosis) and hair changes (coiled body hairs), megaloblastic anemia, poor wound healing, hemorrhagic gingivitis with tooth loss, and occasional emotional changes. Late stages include jaundice, generalized edema, oliguria, neuropathy, fever, convulsions, bone lesions and sudden death. In the infantile form, gingival involvement is minimal and infants assumes a “frog-like” position and do not move their legs due to the pain of subperiosteal hemorrhages.

Although rare in developed countries, outbreaks of scurvy have been reported in select populations such as malnourished refugees/displaced persons, prisoners, alcoholics, and people on unusually restrictive diets. Individuals at higher risk for vitamin C deficiency include:

- Infants who are fed only cow's milk during the first year of life
- Alcoholics and those who conform to food fads
- Elderly and retired people who live alone
- Economically disadvantaged individuals
- Displaced persons/refugees
- Tobacco users (due to decrease absorption of Vitamin C)
- Pregnant and lactating women and those with thyrotoxicosis
- Individuals with anorexia nervosa, advanced acquired immune deficiency syndrome or cancer
- Type 1 diabetics and individuals getting hemodialysis and peritoneal dialysis
- Individuals with diseases of small intestine to include Crohn, Whipple, Celiac Disease.
- Individuals with iron overload diseases.

In the United States, vitamin C deficiency is seen primarily in the poor, the elderly, alcoholics, and in individuals consuming macrobiotic diets. With a diet completely lacking in vitamin C, body pools/stores of vitamin C will last about 2-3 months before symptoms of scurvy arise.

The focus of this review will be on the ethical acceptability of accepting data derived from research studies involving prisoners and pacifist/contentious objectors to support an NDA application. Specifically, I will provide my thoughts on a single trial conducted in subjects that included conscientious objectors (Krebs 1953), and two trials conducted in prisoners [Hodges 1969 and 1971]. The following descriptions of these trials are based on the three articles cited above.

The Krebs article [1953] cited above summarizes a clinical trial done by Professor R. A. Peters at the Sorbey Research Institute in Sheffield, England between 1944 and 1946. The trial involved 19 subjects (18 men and 1 woman), the majority of whom were conscientious objectors. The article does not state how many were conscientious objectors; but, it appears all subjects, regardless of their beliefs, were treated the same with respect to study procedures such as randomization to treatment groups. The article states all subjects were volunteers and "fully aware of the nature of the trial and risks involved." The study report provides evidence subjects were permitted to withdraw consent (one subject withdrew at day 92). The stated objectives of the study included: (1) establish the minimum dose of vitamin C that cures scurvy and (2) correlate the clinical signs of scurvy with laboratory findings. The trial design is not clearly described in the article; however, it appears there were three main phases to the trial. The first phase (preliminary period) involved all subjects receiving a diet that included 70 mg of ascorbic acid. The second phase involved a double blind, placebo control, randomization of subjects into one of 3 groups in which 10 subjects received no vitamin C supplementation, 7 subjects received a supplement of 10 mg of vitamin C, and 3 subjects received a supplement of 70 mg of vitamin C. Otherwise, all subjects received the

same diet that was designed to have < 1 mg of vitamin C/day. The duration of this second phase is unclear, but appears to be at least 424 days for some subjects during which the signs and symptoms of vitamin C deficiency were monitored and recorded. The third phase of the trial involved the replenishment of vitamin C in subjects in order to monitor and record the resolution of the signs and symptoms of vitamin C deficiency. This period seems to have lasted at least 18 weeks. Although the duration of the third phase is not clearly described in the study report, it does clearly state no subject experienced any permanent harm. Study interventions/procedures included a restrictive diet, and repeated blood draws, urine collections, radiographic imaging, ECGs, fatigue studies (not described), and experimental wounding (not described). Additionally, a substudy involving repeated urine collections was done on non-deprived individuals to evaluate vitamin C saturation in the body pool. It appears all subjects were closely monitored and accommodations were made to halt the deprivation phase in subjects experiencing significant adverse events (e.g., 2 subjects experienced chest pain with ECG changes). The study report indicates there was a “committee” that provided oversight of the conduct of this trial; however the scope of their responsibility is not stated.

It should be noted that a number of medical experiments (e.g., scabies transmission, vitamin A deprivation etc.) were carried out on conscientious objectors at Sheffield in addition to the scurvy study described above [Pemberton 2006]. The vitamin C deprivation study was initiated by the Medical Research Council at the request of the Ministry of Food because information was needed to plan for food rationing. The Sheffield studies were funded by the Ministry of Health and the Medical Research Council and were directed by Sir Hans Krebs. 32 men and 3 women volunteered for these studies. None of the volunteers died or had any permanent disability as a result of these experiments according to Pemberton. Most interestingly, Pemberton reports that the three surviving members of this group he was able to identify all stated they thought the experiments had been worthwhile and that they would have volunteered again if required. Additionally, it is interesting to note the group was able to influence the direction of the research by refusing to participate in any experiment in which the main objective was to assist in providing answers to purely military questions. This background information supports the contention that participating in the Sheffield vitamin C deprivation trial could reasonably be considered as voluntary. Similar use of conscientious objectors was done in the United States during World War II [Rosner 2009].

The first study conducted by Hodges [1969] involved six male prisoners from the Iowa State Penitentiary. The stated objectives of the study included: (1) quantify the body pool of ascorbic acid and its rate of depletion during deprivation; (2) estimate the minimal requirements for ascorbic acid; (3) evaluate the relationship of body pool size with clinical signs and symptoms of scurvy; (4) observe the physiological effect of ascorbic acid to include (among other parameters) its effect on wound healing; and (5) determine the amount of ascorbic acid necessary to replete the body pool and alleviate clinical signs of scurvy. The article states all subjects were volunteers. Once identified, all subjects were housed in the Metabolic Ward of the University Hospitals in Iowa City and closely monitored for the duration of the study. The study design, as described in the 1969 article, suggests there were 2 major phases to the trial. In the first phase (deprivation phase, Day 1 to 99), subjects self-administered through a gastric tube, a liquid diet devoid of ascorbic acid three times daily.

This diet was administered until “*convincing evidence of mild clinical scurvy appeared.*” The threshold used for defining “mild clinical scurvy” is not provided in the article; however, reported signs and symptoms of scurvy included hyperkeratosis, congestion of follicles, petechial rash, conjunctival lesions, sublingual hemorrhages, swollen gums, and papillary swelling. Most findings were rated as either 1 or 2 on a four point scale with a few noted exceptions. The following adverse events were rated as 4 by one patient each: hyperkeratosis, swollen gums, follicular congestion, and papillary swelling. The second phase of the study (repletion phase) involved active administration of ascorbic acid at various doses until all evidence of scurvy resolved. The author reports this phase as starting on Day 100. After two weeks of ascorbic acid repletion the liquid diet was changed to a modified solid diet. The article provides few details on the resolution of symptoms; however, it appears subjects were followed to at least day 200, possibly 220. Study interventions/procedures appear to include a repeated blood draws for a variety of analyses, urine and stool collections, restricted liquid diet administered by gastric tube, radiographic imaging, serial ECGs, serial EEGs, and physical activity (10 mile walks/day). Additionally, a wound healing assessment test was done early in the repletion phase that involved making a 5 cm surgical wound in the left thigh which was closed with suture and subsequently biopsied using a punch biopsy to assess for histological changes. The study report indicates there was some level of oversight done by an external group during the conduct of this trial (e.g., “permission” needed to be obtained to administer radiolabeled vitamin C); however, the scope of this oversight is not discussed.

The second study conducted by Hodges [1971] involved six male prisoners from the Iowa State Penitentiary. The stated objectives of the study included: (1) quantify the body pool of ascorbic acid, (2) evaluate the catabolism of ascorbic acid, (3) assess the correlation between body pool size and blood plasma levels, and (4) evaluate the relationship of body pool size, catabolism, and plasma levels with clinical signs and symptoms of scurvy. The article states that informed consent was obtained in all subjects and there is evidence that subjects were permitted to withdraw (1 subject withdrew). Once identified, all subjects were housed in the Metabolic Ward of the University Hospitals in Iowa City and closely monitored for the duration of the study. The study design, as described in the 1971 article, suggests there were 3 major phases to the trial. The first phase (day 1 to 13) was a control period in which all subjects were fed a diet rich in ascorbic acid. The second phase involved a strict diet that had essentially no ascorbic acid. This deprivation phase continued until the subjects had “evidence of clinical scurvy.” The threshold used for defining “clinical scurvy” is not provided in the articles; however, it appears some subjects were allowed to develop significant clinical manifestations of scurvy to include femoral neuropathy and joint effusions. The duration of time for the deprivation phase ranged from 84 to 97 days. During the deprivation phase a single person withdrew consent prior to the development of clinical scurvy. No other details on this withdrawal are described. The final phase involved the active administration of ascorbic acid at various doses until all evidence of scurvy resolved. The study report states that recovery was complete 4 months after the beginning of treatment with ascorbic acid. In total it appears subjects were followed for approximately 8 to 9 months. Study interventions/procedures appear to include repeated blood draws for a variety of analyses, urine and stool collections, restricted diets, radiographic imaging, ECGs, serial ophthalmology evaluations, repeated expired air collection, a vaccine re-challenge (Typhus),

psychomotor performance testing, and a cold climate exposure (50° F for 4 hours on day 112-115).

III. Regulatory/Ethical Review

The issue of whether the FDA should accept data from studies conducted in situations such as what occurred in the trials described above is complex and requires a close review of the circumstances surrounding the trials in question and an understanding of the historical context in which the trials were conducted. Unfortunately, we have limited information on these trials (e.g., no source documentation, no informed consent documents, etc.) and as such my recommendations will be based on incomplete data.

With respect to historical context, it must be remembered that at the time these studies were conducted there was true clinical equipoise with respect to what was the appropriate minimal daily dose of ascorbic acid necessary to prevent and treat scurvy. Likewise, the question about optimal dose for nutritional supplements was particularly important during the conduct of the 2nd World War, and the period following due to the prolonged deployments of troops to environments with uncertain supply lines and the displacement of a large number of people to locations with limited resources available, all of which created an environment that was ripe for major outbreaks of diseases associated with nutritional deficiencies. Similarly, it must be remembered that the ethical standards for the conduct of clinical trials that we know today either did not exist during the time these trials were conducted or were not widely adopted. In the past, the FDA, when confronted with the question as to whether to accept data from old studies that may not have satisfied our current regulatory and ethical standards, we have assessed each case individually and typically judged them by the standards that existed at the time the trials were conducted. I will take this approach.

A discussion about the evolution of our ethical and regulatory standards for the conduct of clinical research is beyond the scope of this review; however, the following historical milestones should be considered:

- 1947: Nuremberg Code issued as a response to the Nazi Doctor Trials.
- 1967: Declaration of Helsinki issued (multiple revisions have since occurred).
- 1978: U.S. DHHS (previously HEW) issued the first U.S. regulations governing the protection of prisoners who participate in research (incorporated as Subpart C in 45 CFR 46).
- 1979: Belmont Report issued. This report developed out of the U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Our current ethical and regulatory standard for the protections of human subjects volunteering for research is based on the three principles outlined in the Belmont Report (respect for persons, beneficence, and justice).
- 1981: U.S. DHHS issued 45 CFR 46 (subpart A) outlining the regulatory requirements for the protection of human subjects participating in research (analogous regulations issued by FDA in 1980 and 1981).

The Sheffield study predates all of these codes. Similarly, the prisoner studies conducted by Hodges predate the Belmont Report and the DHHS/FDA regulations and either predate or

were ongoing when the Declaration of Helsinki was issued. As such the key ethical codes to consider for the prisoner studies are the Nuremberg Code and perhaps the first Declaration of Helsinki.

The [Nuremberg Code](#) outlines 10 principles related to the protection of subject involved in research. Key amongst these principles for this review and analysis are principles (1) *“the voluntary consent of the human subject is absolutely essential”*; (2) *“the experiment should be such as to yield fruitful results for the good of society”* and (10) *“...human subjects should be at liberty to bring the experiment to an end, if he has reached the physical and mental state, where continuation of the experiment seemed to him to be impossible.”* The Code does not specifically address the conduct of research in prisoners or conscientious objectors; however, the principles contained in the Code are reasonable to consider for these populations. As described above, it appears voluntary consent was obtained from all subjects, the goal of the trials were for the good of society, and there is evidence that subjects were free to withdraw from the trial when they wanted to stop participating in the research. As such, it appears these three principles in the Nuremberg Code have been satisfied. The other principles also appear to have been satisfied, but for simplicity will not be summarized here as they relate more to the safety and the conduct of the trial rather than the goal of the trial and the willingness of the participants. The trials, as described in the reports, appear to have been reasonably safe and adequately conducted. It appears all subjects were closely monitored and all subjects were followed until complete resolution of their scurvy symptoms.

Like the Nuremberg Code, the 1964 version of the [Declaration](#) of Helsinki (DOH) emphasized the need to assure the willingness of subjects to participate in research and the need for the goal of the research to be of sufficient importance to justify the inherent risk to subject. As with the Nuremberg Code, the 1964 DOH does not specifically address research involving prisoners or conscientious objectors. However, unlike the Nuremberg Code, the 1964 DOH expressly states that consent *“should as a rule be obtained in writing.”* Although the articles cited above clearly indicate that subjects were volunteers and suggest they were fully informed of the risks, there is no clear statement as to whether consent was obtained in writing. This does not mean that signed informed consent was not obtained; in fact one of the prisoner study reports [Hodges 1971] does states *“informed consent was obtained”* which could be interpreted as meaning that it was documented. The DOH does not clarify when it would be reasonable to not obtain consent in writing; however, it indicates there may be exceptions. The current HHS regulations at 45 CFR 46 (and the analogous FDA regulations) states that the documentation of consent can be waived when research is determined to be no more than minimal risk to the subject and involves no procedures for which written consent is normally required outside the research context (see 21 CFR 56.109(c) and 45 CFR 46.117(c)(2)). If we were to apply the current regulatory requirements to these trials we would not permit a waiver of documentation because the research was clearly greater than minimal risk; however, it is unreasonable to expect research conducted decades ago to satisfy all the current regulatory requirements. Similarly, it may be unreasonable to apply the requirements of the DOH to these studies given that the Sheffield Experiment occurred over 2 decades prior to the issuance of the DOH and the Iowa State prisoner studies were either ongoing or started soon after the issuance of the DOH.

Another way to evaluate whether these trials should be accepted by the FDA for regulatory decisions is to evaluate them in the context of past determinations involving similar situations. Although each case should be evaluated on its own merits, it is not unreasonable to consider the position taken on past cases in which we were asked to opine on the acceptability of data that may not have met current regulatory standards. I am unaware of any past examples in which the ethics group (adult or pediatric) was asked to opine on the acceptability of questionable research involving prisoners. However, my predecessor did opine on the acceptability of accepting data from old research conducted in conscientious objectors. Specifically, my colleague was asked to opine of accepting data from “Operation White Coat” which involved 150 trials in which over 2300 recruits from the Seventh Day Adventist were exposed to a variety of infectious diseases from 1954 to 1973. As I am doing in this review, she considered the issue through the lens of the standards that existed at the time the research was conducted. The documentation my previous colleague was able to obtain about the consent process and her understanding that conscientious objectors had other options related to serving (e.g., combat medic, cook etc.) assured her that the consent was voluntary and she recommended the data be accepted. Although I do not have the source documents associated with the Sheffield and Hodge trials, or complete details on the informed consent process; based on the published articles, it appears participation in the Sheffield and Hodges studies was voluntary, informed consent was obtained, subjects were informed of the risks, and subjects were permitted to withdraw. The fact that the studies had individuals who withdrew provides supporting evidence that there was no coercion or undue influence. That being said, contemporary understanding of undue influence in the prison population has evolved over the past several decades such that there is a greater understanding that undue influence in prisoners may include subtle factors such as seemingly minor payments that takes on greater importance for prisoners and changes in the nature of their incarceration (e.g., special treatment, better food, etc.). The fact that prisoners in the Hodge studies were housed in a hospital for over a year could possibly be considered as undue influence today but was likely not considered such in the mid-20th century.

Since 1978, prisoners have been considered a uniquely vulnerable population and have been afforded, as a class, additional regulatory protections for biomedical and behavioral research supported or conducted by DHHS (see [45 CFR 46 subpart C](#)). Although FDA does not have analogous regulatory requirements that apply to prison research, we often do consider the standards contained in the DHHS regulations when we consider the ethical underpinnings of research involving prisoners. However, from a strict compliance sense we would not apply subpart C regulations to research submitted to the FDA unless that research was supported or conducted by DHHS. With that stated, it is a useful exercise to briefly consider the following unique protections contained in Subpart C even though they should not be applied to the prison studies described by Hodges (requirements paraphrased):

- The majority of the Institutional Review Board (IRB) members must not be associated with the prison and at least one member of the IRB must be a prisoner, or a prisoner representative
- The research is limited to:
 - Study of possible causes, effects, and processes of incarceration, and of criminal behavior, provided the research is no more than minimal risk and no more than inconvenience to the prisoner

- Study of prisons or of prisoners as incarcerated persons so long as the research is no more than minimal risk and no more than inconvenience to the prisoner
- Research on conditions particularly affecting prisoners as a class provided the study may proceed only after the Secretary has consulted with appropriate experts and published notices in the Federal Register
- Research on practices which have the intent and reasonable probability of improving the health or well-being of the subject. If the research involves the use of a control group in which subjects may not benefit (e.g., placebo) the research must be submitted to the Secretary for review by a panel of experts and be published in the Federal Register.
- The IRB must assure that any possible advantage accruing to the prisoner is not of such magnitude that it impairs the prisoner's ability to weigh the risks of the research (this includes general living conditions, medical care, quality of food etc.)
- The research risks are commensurate with risks that non-prisoner volunteers would find acceptable
- Parole decisions must not be influenced by participating in the research and prisoners must be told of this fact in advanced or participating
- Assurances exists that any necessary follow up care after participation will be available
- The Institute must certify to the Secretary (OHRP) that the duties of the IRB have been fulfilled.

A review of these regulatory requirements clearly demonstrates that the studies described by Hodges would not meet the regulatory standards that exist today. These regulations have greatly reduced the volume and scope of research conducted in U.S. prisons to the point that some are now advocating loosening the restrictions to allow for a greater variety of research to be conducted in prisoners [Coughlin 2016, Gostin 2007].

10/27/2016: Addendum:

In response to an information request the sponsor provided additional details regarding the informed consent process and oversight that occurred in the two prisoner studies cited above. Additionally, the sponsor provided a 1967 article by Dr. Hodges in which he reflects on the ethical implications of the research he has done in prisoners [Hodges 1967]. Based on the additional details provided in the information request, it is clear that the prison studies conducted at Iowa State Penitentiary included the use of a written informed consent and that volunteers were free to withdraw from the research "at any time." Similarly, it appears that oversight for the trials conducted at Iowa State prison were provided by prison officials the Board of Control, and the research committee of the College of Medicine. Additionally Dr. Hodges, in his 1967 article, notes that Iowa State law (as of 1963) mandated that consent from prisoner be in writing and an assurance that inmates may withdraw their consent at any time.

IV. Conclusion

Based on the materials provided, published literature cited above, and my analysis outlined above, it appears the Sheffield and Hodges studies listed above were designed and conducted

in a manner consistent with the ethical standards for human subject protections that existed at the time the trials were conducted. Overall it appears participation in the Sheffield and Hodges studies was voluntary, informed consent was obtained, subjects were informed of the risks, and subjects were permitted to withdraw. Additionally, it appears that subjects were closely followed to assure safety and that all subjects were adequately followed until all symptoms of scurvy resolved. However, without access to study documents such as the final protocol, the informed consent document, and other source documents, it is not possible to confirm what is described in the Sheffield and Hodge articles truly reflect what occurred during these trials. Although these trials would not meet the standards for human subject protections expected of clinical investigations conducted today, I do believe it is ethically acceptable to use the data from these trials in the evaluation of a new drug application.

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/s/

KEVIN A PROHASKA
10/27/2016