CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209112Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 209112	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Ascor Established/Proper Name: ascorbic acid Dosage Form: injection		Applicant: McGuff Pharmaceuticals, Inc. Agent for Applicant (if applicable): NA
RPM: Abolade (Bola) Adeolu		Division: Metabolism & Endocrinology Products

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

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

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

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

☒ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check: 9.26.2017

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

❖ Actions	
• Proposed action • User Fee Goal Date is 10.2.2017	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

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

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): Type 7- Drug Already Marketed without Approved NDA
(confirm chemical classification at time of approval)

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

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

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

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

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

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

Comments:

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

CONTENTS OF ACTION PACKAGE

Officer/Employee List

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

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action and date: 10.2.2017
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included – See labeling attached to approval letter
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included – See labeling attached to approval letter
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Granted letter: 11.18.2016 Review: 11.8.2016
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ 10.31.2016 DMEPA: ☒ 3.16.2017 DMPP/PLT (DRISK): ☐ OPDP: ☒ 8.22.2017 SEALD: None CSS: None Product Quality: None Other: None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	10.31.2016 9.28.2018
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

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

• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC No Review If PeRC review not necessary, explain: Orphan Designation (#07-3437 on 8.31.2007)	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	Included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A
• Pre-NDA/BLA meeting *(indicate date of mtg)*	IND 076483- WRO granted and Meeting minutes issued 9.22.2011
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☒ None
Cross-Discipline Team Leader Review *(indicate date for each review)*	10.02.2017
PMR/PMC Development Templates *(indicate total number)*	☒ None

Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	9.28.2017
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☒ and include a review/memo explaining why not *(indicate date of review/memo)*	Page 11 of clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☐ None DPMH – 9.20.2017, 9.19.2017
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	8.29.2017
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

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

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	8.29.2017
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	8.18.2017
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	8.18.2017
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable ☐ Withhold recommendation ☐ Not applicable

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

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

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/s/

ABOLADE ADEOLU
10/02/2017

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Friday, September 08, 2017 2:59 PM
To: 'Joe Kosnosky'
Cc: Damon Jones; Adeolu, Abolade
Subject: RE: request for update NDA 209112

Importance: High

Joe-

I have attached the PI for Ascor with our first round of comments. Please accept the changes you agree with, and provide comments on changes you do not agree with. Update PI and return to us by COB Wednesday, September 13, 2017.

Thanks,

Bola Adeolu
301 796-4264

From: Joe Kosnosky [mailto:jkosnosky@mcguff.com]
Sent: Thursday, September 07, 2017 7:21 PM
To: Adeolu, Abolade
Cc: Damon Jones
Subject: RE: request for update NDA 209112

Hello Bola,
Was the labeling review meeting held today? Will MPI receive a summary of the outcome on Friday 9/8?

Very Best Wishes,

Joe Kosnosky
Sr. Regulatory Affairs Specialist
2921 West MacArthur Blvd., Suite 141
Santa Ana, CA 92704
Phone: 800-603-4795 Ext. 340
Email: jkosnosky@mcguff.com
Web: mcguff.com

From: Adeolu, Abolade [mailto:Abolade.Adeolu@fda.hhs.gov]
Sent: Tuesday, August 22, 2017 9:20 AM
To: Joe Kosnosky

Cc: Damon Jones
Subject: RE: request for update NDA 209112

Working on PI. Labeling meeting on Sept 7. Will send on that day or Sept.8. Once you receive PI, please remember you still need to address the carton/container comments sent March, 17, 2017.

thanks

Bola Adeolu
301 796-4264

From: Joe Kosnosky [mailto:jkosnosky@mcguff.com]
Sent: Tuesday, August 22, 2017 11:57 AM
To: Adeolu, Abolade
Cc: Damon Jones
Subject: request for update NDA 209112

Hello Bola,
As we approach the end of month 2 of the three month review extension for NDA 209112 (PDUFA date October 2, 2017), can you provide any update on when FDA will provide labeling comments?

Very Best Wishes,

Joe Kosnosky
Sr. Regulatory Affairs Specialist
2921 West MacArthur Blvd., Suite 141
Santa Ana, CA 92704
Phone: 800-603-4795 Ext. 340
Email: jkosnosky@mcguff.com
Web: mcguff.com

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

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/s/

ABOLADE ADEOLU
09/11/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209112

**REVIEW EXTENSION –
MAJOR AMENDMENT**

McGuff Pharmaceuticals, Inc.
Attention: Damon P. Jones
Vice President and Director of Operations
2921 W. MacArthur Blvd, Suite 141
Santa Ana, CA 92704-6929

Dear Mr. Jones:

Please refer to your New Drug Application (NDA) dated and received September 2, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ascorbic acid injection 500 mg/mL.

On June 12, 2017, we received your June 9, 2017, major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is October 2, 2017.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA Reauthorization Performance Goals and Procedures – Fiscal Years 2013 through 2017." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by September 11, 2017.

If you have any questions, call Abolade (Bola) Adeolu, Regulatory Project Manager, at (301) 796-4264.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, MD
Director
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JEAN-MARC P GUETTIER
06/19/2017

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Monday, May 01, 2017 2:47 PM
To: Joe Kosnosky (jkosnosky@mcguff.com)
Cc: Adeolu, Abolade
Subject: NDA 209112

Dear Joe,

We conducted the review of the labeling and have the following comments/requests:

- Remove the "Pharmacy Bulk Package" and replace it with a "single dose vial" throughout the label.
- In Section 2, indicate the following:
  a. Ascorbic Acid Injection is for single dose only (up to 1 ml).
  b. Any unused portion must be discarded immediately.
-

Submit the updated label by the end of the week.

Thanks,
Bola

Bola Adeolu, R.Ph., MS, MBA
Senior Regulatory Project Manager,
FDA/CDER/OND
Division of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3121
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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/s/

ABOLADE ADEOLU
05/01/2017

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Monday, March 27, 2017 2:05 PM
To: Joe Kosnosky (jkosnosky@mcguff.com)
Cc: Adeolu, Abolade
Subject: NDA 209112

Joe-

We have the following comment and expect a response by April 10, 2017-

It is unclear why you plan to package Ascorbic Acid as a Pharmacy Bulk Package for the proposed indication, i.e. treatment of scurvy. Given that the (b) (4) single dose to be recommended for this product is (b) (4) which can be given in (b) (4) we are concerned that the large 50mL bottles will lead to significant safety issues, such as dosing errors, misusing of the drug, multiple entry into a container which contains no preservative. Please justify the need for the current packaging for the proposed indication (i.e. treatment of scurvy). Unless you can justify the need for the current packaging we recommend that you repackage the formulation in smaller single use vials.
Such repackaging should lower the risk of the larger bottles exploding from increased pressure as well.

Kindly acknowledge receipt of this email.

Best,
Bola

Bola Adeolu, R.Ph., MS, MBA
Senior Regulatory Project Manager,
FDA/CDER/OND
Division of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3121
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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/s/

ABOLADE ADEOLU
03/27/2017

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Friday, March 17, 2017 11:05 AM
To: Joe Kosnosky (jkosnosky@mcguff.com)
Cc: Hamilton-Stokes, Deveonne; Adeolu, Abolade
Subject: NDA 209112: Labeling

Joe,

We recommend the following be implemented and submitted by April 7, 2017:

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.
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.

Thanks,
Bola

Bola Adeolu, R.Ph., MS, MBA
Senior Regulatory Project Manager,
FDA/CDER/OND
Division of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3121
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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/s/

ABOLADE ADEOLU
03/17/2017

From: Lalmansingh, Anika
To: "Joe Kosnosky"
Cc: Adeolu, Abolade
Subject: RE: NDA 209112 - Questions regarding Filing Communication
Date: Friday, December 16, 2016 8:51:00 AM
Attachments: image001.png
image002.png

Hello Joe,

We acknowledge receipt of your responses to the FDA Filing Communication, dated December 14, 2016, in which you included a written response or teleconference with FDA to discuss requested labeling changes.

We are denying the request because labeling issues will be discussed internally by the FDA review team. Once that is done, comments will be conveyed to you during the labeling negotiations.

If you have any questions, feel free to contact me.

Kind Regards.
-Anika

Regulatory Business Process Manager
Center for Drug Evaluations and Research (CDER)
Office of Pharmaceutical Quality (OPQ)
U.S. Food and Drug Administration
Tel: 240-402-0356

From: Joe Kosnosky [mailto:jkosnosky@mcguff.com]
Sent: Monday, December 12, 2016 9:45 PM
To: Lalmansingh, Anika
Cc: Adeolu, Abolade
Subject: RE: NDA 209112 - Questions regarding Filing Communication

Hello Anika,
I expect that the Amendment will be submitted by Dec. 15 and can notify you post-submission.

After discussion with Ms. Adeolu, in the cover letter and in the MPI Response I will include a request for an Agency written response or telecon on this issue.

Thank you for your assistance on this issue.

Very Best Wishes,

Joe Kosnosky
Sr. Regulatory Affairs Specialist

McGUFF Pharmaceuticals, Inc.

TOP WORK PLACES 2015 ORANGE COUNTY REGISTER

2921 West MacArthur Blvd., Suite 141
Santa Ana, CA 92704
Phone: 800-603-4795 Ext. 340
Email: jkosnosky@mcguff.com
Web: mcguff.com

From: Lalmansingh, Anika [mailto:Anika.Lalmansingh@fda.hhs.gov]
Sent: Monday, December 12, 2016 2:28 PM
To: Joe Kosnosky
Cc: Adeolu, Abolade
Subject: RE: NDA 209112 - Questions regarding Filing Communication

Hello Joe,

We request that you include everything in this email as the response to FDA's questions 1-3 from the Filing Communication. We will then evaluate this information as part of our review of the entire response. If we have any further questions, we will send them to you after our complete review.

Feel free to let me know if you have any additional questions/concerns.

Kind Regards.
-Anika

Regulatory Business Process Manager
Center for Drug Evaluations and Research (CDER)
Office of Pharmaceutical Quality (OPQ)
U.S. Food and Drug Administration
Tel: 240-402-0356

From: Joe Kosnosky [mailto:jkosnosky@mcguff.com]
Sent: Monday, December 12, 2016 1:05 PM
To: Lalmansingh, Anika
Cc: Adeolu, Abolade
Subject: RE: NDA 209112 - Questions regarding Filing Communication

Hi Anika,
After some additional thought and a discussion with the NDA Project Manager, I would like request a telecon to discuss the FDA requested changes to drug product nomenclature. Because this issue affects both the CMC and requests for changes to the labeling, MPI would like to discuss this issue with FDA and come to agreement so that any User Fee Goal

dates are not negatively impacted. Because there is a due date of December 15 for our response to the Filing Communication, could you provide a reply prior to Dec 15?

With regard to the Filing Communication (ID 4006792), FDA stated that the product is sodium ascorbate, not ascorbic acid. Comments #1-3 directed MPI to revise Module 3 and labeling.

MPI disagrees that the nomenclature should change and provides the following comments:

After review of historical commercial availability and clinical use of the drug product named 'Ascorbic Acid Injection', MPI believes that renaming the drug product to 'Sodium Ascorbate for Injection' would be a significant departure from market and clinical expectations and there is a danger that this could lead to medication errors. However, MPI proposes several changes to the proposed Package Insert to provide additional information and clarity on the drug product formulation and safety.

1. The expected name of this product is based on the amount of Active Pharmaceutical Ingredient utilized in the formulation. In this case, Ascorbic Acid, USP is utilized as the drug substance in the formulation, not Sodium Ascorbate, USP, and the drug product is intended to comply with the USP monograph for Ascorbic Acid Injection, USP (There is no USP monograph for Sodium Ascorbate Injection).

   Because there is an expectation in the clinical community that the strength of the product is based on Ascorbic Acid (500 mg/mL) and dosing is typically determined based on an amount of ascorbic acid to be delivered, a change in the nomenclature and/or stated strength could lead to confusion and potential medication errors. It could also lead to misbranding . Clinical references utilized by the medical community (e.g., American Society of Hospital Pharmacists Handbook on Injectable Drugs, Facts and Comparisons, DailyMed) refer to treatment doses based on amounts of ascorbic acid provided.

   In addition, a survey of relevant current clinical trials on clinicaltrials.gov is inconsistent with regard to nomenclature, referring to drug products as Vitamin C, Ascorbic Acid, or Ascorbate. It does appear however that dose regimens are based on concentration of Ascorbic Acid delivered to trial subjects.

2. In addition, the nomenclature proposed by MPI would also comply with FDA guidelines (Guidance document 'Naming of Drug Products Containing Salt Drug Substances'; June 2015 and MAPP 5021.1 'Naming of Drug Products Containing Salt Drug Substances') in which the following two applicable statements are

included:

a. When the USP Salt Policy becomes official on May 1, 2013, USP will apply it only to new drug product monograph titles. *The names of published drug product monograph titles should not change* unless necessary for reasons such as safety. USP and FDA have agreed to coordinate on any retrospective name changes. [emphasis added]

b. *If there is an existing USP drug product monograph title, that title in most instances serves as the nonproprietary name of the related drug product.* A product with a nonproprietary name that is not consistent with the applicable monograph title risks being misbranded. [emphasis added]

3. MPI proposes two changes to the current Package Insert and primary/secondary package labeling to provide additional information for the clinician:

a. To provide a statement in the Description Section for the equivalence of sodium ascorbate to ascorbic acid to read "Each mL contains 500 mg of ascorbic acid, (equivalent to 562.5 mg of sodium ascorbate).

b. To include a [redacted] (b) (4)

I appreciate your attention to this matter. Would it be possible for you to call me to discuss this issue and how it can be resolved?

Very Best Wishes,

Joe Kosnosky
Sr. Regulatory Affairs Specialist
2921 West MacArthur Blvd., Suite 141
Santa Ana, CA 92704
Phone: 800-603-4795 Ext. 340
Email: jkosnosky@mcguff.com
Web: mcguff.com

From: Lalmansingh, Anika [mailto:Anika.Lalmansingh@fda.hhs.gov]
Sent: Friday, December 09, 2016 5:34 AM

To: Joe Kosnosky
Subject: RE: NDA 209112 - Questions regarding Filing Communication

Your welcome Joe. Have a nice weekend.

-Anika

Regulatory Business Process Manager
Center for Drug Evaluations and Research (CDER)
Office of Pharmaceutical Quality (OPQ)
U.S. Food and Drug Administration
Tel: 240-402-0356

From: Joe Kosnosky [mailto:jkosnosky@mcguff.com]
Sent: Thursday, December 08, 2016 8:07 PM
To: Lalmansingh, Anika
Subject: RE: NDA 209112 - Questions regarding Filing Communication

Hello Anika,
Thank you for your feedback. The clarification that was provided is sufficient for us to prepare our response and we will not request a telecon at this time.

Very Best Wishes,

Joe Kosnosky
Sr. Regulatory Affairs Specialist
2921 West MacArthur Blvd., Suite 141
Santa Ana, CA 92704
Phone: 800-603-4795 Ext. 340
Email: jkosnosky@mcguff.com
Web: mcguff.com

From: Lalmansingh, Anika [mailto:Anika.Lalmansingh@fda.hhs.gov]
Sent: Wednesday, December 07, 2016 11:56 AM
To: Joe Kosnosky
Subject: NDA 209112 - Questions regarding Filing Communication

Good afternoon Joe,

Bola has informed me that you and your CMC team would like a Tcon regarding FDA's questions 1, 2, and 3 of the Filing Communication.

In order to consider your meeting request, provide to me in writing the specific issues/concerns that you have regarding these questions. In FDA's questions 2 and 3, "formulation" refers to concentrations of components in the final drug product.

Kind Regards.

-Anika

Anika Lalmansingh, PhD
Regulatory Business Process Manager

Center for Drug Evaluations and Research (CDER)
Office of Pharmaceutical Quality (OPQ)
U.S. Food and Drug Administration
Tel: 240-402-0356
anika.lalmansingh@fda.hhs.gov

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/s/

ANIKA A LALMANSINGH
12/16/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209112

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

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

ATTENTION: Damon P. Jones
Vice President and Director of Operations

Dear Mr. Jones:

Please refer to your New Drug Application (NDA) dated and received September 2, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ascorbic Acid Injection, 500 mg/mL.

We also refer to your correspondence, dated and received September 16, 2016, requesting review of your proposed proprietary name, Ascor.

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

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

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

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

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Deveonne Hamilton-Stokes, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology at (301) 796-2253. For any other information regarding this application, contact Abolade Adeolu, Regulatory Project Manager, in the Office of New Drugs at (301) 796-4264.

Sincerely,

{See appended electronic signature page}

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

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/s/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
11/18/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209112

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

McGuff Pharmaceuticals, Inc.
Attention: Damon P. Jones
Vice President and Director of Operations
2921 W. MacArthur Blvd, Suite 141
Santa Ana, CA 92704

Dear Mr. Jones:

Please refer to your New Drug Application (NDA) dated August 31, 2016, received September 2, 2016, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for sodium ascorbate for injection.

We also refer to your amendments dated September 16, 21 and October 5, 2016.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is July 2, 2017.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 4, 2017.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information by **December 15, 2016**:

Chemistry, Manufacturing, and Controls

1. Based on the information in the NDA on the drug concentration and pH range, your product is "sodium ascorbate", not "ascorbic acid". It is not clear whether the labeled drug concentration and strength correspond to the acid or the salt. Revise all labeling to state the correct non-proprietary drug name of the product and the corresponding drug concentration and strength.

2. Revise the composition statement in Module 3 to include actual amounts of product components present in the formulation (i.e., actual amounts per mL of sodium ascorbate, ascorbic acid, sodium bicarbonate, sodium hydroxide used as (b) (4), edetate disodium (b) (4)

3. Revise the prescribing information (PI) and container/carton labels to indicate the actual amounts product components present in the formulation (i.e., actual amounts per mL of sodium ascorbate, ascorbic acid, sodium bicarbonate, sodium hydroxide used as (b) (4), edetate disodium (b) (4).

4. The NDA includes compatibility data for the dilution of the product in 5% dextrose and SWFI. Provide compatibility data in support of the labeled instructions to dilute the product using (b) (4)

5. Based on the compatibility studies and stability data of the diluted product, revise the Dosage and Administration section of the PI to state the amount of each diluent and the maximum in-use (i.e., infusion) time of the diluted product.

6. We note that the PI includes the instructions to have " (b) (4) " and to discard the unused portion within 4 hours. The (b) (4) daily dose is proposed to be (b) (4), which is (b) (4) of the product. Explain why the product (without preservative) is packaged with the strength of 25 g in a 50 mL volume.

7. We note that the elemental impurities risk assessment for the drug product as per ICH Q3D "Elemental Impurities" is currently ongoing. Provide a timeline for the assessment completion and submission of the report to the NDA.

8. Submit the master batch records as required by 21 CFR 314.54 for a 505(b)(2) application.

9. Provide historical batch data to support the product pH range of (b) (4) Citing the USP monograph as justification for this wide range is not sufficient because the regulatory drug product specification should be product-specific.

Clinical Pharmacology

10. Provide appropriate justification and relevant references to support your proposed dosing recommendations for adults and pediatric subjects. Also provide detailed information and references on the drug interactions of ascorbic acid (e.g. with warfarin, (b) (4), etc.).

PRESCRIBING INFORMATION

Your proposed PI must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

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

On December 4, 2014, the Food and Drug Administration published the "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling," also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR went into effect on June 30, 2015. According to PLLR, Risk Summary statements for sections 8.1 (Pregnancy), 8.2 (Lactation), and 8.3 (Females and Males of Reproductive Potential) must be based on available human and nonclinical data. The Risk Summary must also state when there are no human data or when available human data do not establish the presence or absence of drug-associated risk (21 CFR 201.57(c)(9)(i)(B)(1)).

Together with submission of the proposed labeling for PLLR compliance, applicants should provide the following information to support the labeling content: a review and summary of the relevant published literature, summary of cases reported in the pharmacovigilance database, interim ongoing or final report on a closed pregnancy registry (if applicable).

During our preliminary review of your submitted labeling, we found that you did not submit proposed labeling for PLLR compliance, nor did you provide a review and summary of the available literature to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. Thus, your proposed PLLR labeling changes cannot be agreed upon until the information request is fulfilled. No partial PLLR conversions may be made.

We request that you resubmit labeling (in Microsoft Word format) that addresses PLLR and submit the following information on ascorbic acid use in pregnant and lactating women by **December 15, 2016**:

- a review and summary of all available published literature regarding ascorbic acid,

- a review and summary from your pharmacovigilance database, interim ongoing or final report on a closed pregnancy registry (if applicable),
- a revised labeling, if appropriate, incorporating the above information (in Microsoft Word format) that complies with PLLR.

Refer to the Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf). Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments. Please submit revised labeling addressing these comments by **December 15, 2016**:

a. Remove [redacted] (b) (4) which appears at the top of Highlights.

b. The length of Highlights should be one-half page, otherwise a waiver should be requested.

c. There should be a horizontal line between Table of Contents and Full Prescribing Information.

d. There should not be white space between Highlights heading and Highlights limitation statement.

e. There should be no white space between Product title and Initial US approval.

f. Name of drug not consistent in the Highlights Limitation statement.

g. The line on either side of FULL PRESCRIBING INFORMATION title should be be deleted.

h. [redacted] (b) (4) should be deleted

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

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

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

Because the drug product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Abolade (Bola) Adeolu, Regulatory Project Manager, at (301) 796-4264.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, MD
Director
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JEAN-MARC P GUETTIER
11/02/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209112

INFORMATION REQUEST

McGuff Pharmaceuticals, Inc.
Attention: Damon P. Jones
Vice President and Director of Operations
2921 W. MacArthur Blvd., Suite 141
Santa Ana, CA 92704

Dear Mr. Jones:

Please refer to your New Drug Application (NDA) dated August 31, 2016, received September 2, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ascorbic acid injection.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response **October 14, 2016** in order to continue our evaluation of your NDA.

Regarding the use of the following control testing laboratories, please submit an updated 356h form and provide details of the proposed testing that will be conducted at each of the following facilities for the types of samples submitted, such as identity testing, particulate matter testing, or microbial limits testing:

If you have any questions, please contact Anika Lalmansingh, Regulatory Business Process Manager at (240) 402-0356.

Sincerely,

{See appended electronic signature page}

Suong Tran, PhD
Quality/CMC Lead
Division of New Drug Products II
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

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/s/

SUONG T TRAN
09/30/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209112

PROPRIETARY NAME ACKNOWLEDGEMENT

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

ATTENTION: Damon P. Jones
Vice President and Director of Operations

Dear Mr. Jones:

Please refer to your New Drug Application (NDA) dated and received September 2, 2016, submitted under 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ascorbic Acid Injection, 500 mg/mL.

We acknowledge receipt of your correspondence, dated and received September 16, 2016, requesting a review of your proposed proprietary name, Ascor.

If the application is filed, the user fee goal date will be December 15, 2016.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Deveonne Hamilton-Stokes, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology at (301) 796-2253. For any other information regarding this application, contact Abolade Adeolu, Regulatory Project Manager, in the Office of New Drugs at (301) 796-4264.

Sincerely,

{See appended electronic signature page}

Deveonne Hamilton-Stokes, RN, BSN, MA
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DEVEONNE G HAMILTON-STOKES
09/28/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209112

NDA ACKNOWLEDGMENT

McGuff Pharmaceuticals, Inc.
Attention: Damon P. Jones
Vice President and Director of Operations
2921 W. MacArthur Blvd, Suite 141
Santa Ana, CA 92704

Dear Mr. Jones:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: ascorbic acid injection 500 mg/ mL

Date of Application: August 31, 2016

Date of Receipt: September 2, 2016

Our Reference Number: NDA 209112

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 1, 2016, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory

registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information for registering your clinical trials is available at the Protocol Registration System website http://prsinfo.clinicaltrials.gov/.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 209112** submitted on September 2, 2016, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism & Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-4264.

Sincerely,

{See appended electronic signature page}

Abolade (Bola) Adeolu, RPh, MS, MBA
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

ABOLADE ADEOLU
09/14/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

PIND 076483

MEETING REQUEST - Written Responses

McGuff Pharmaceuticals, Inc.
Attention: Joseph Kosnosky, RAC
Sr. Regulatory Affairs Specialist
2921 W. MacArthur Blvd.
Suite 141
Santa Ana, CA 92704-6929

Dear Mr. Kosnosky:

Please refer to your Pre-Investigational New Drug Application (PIND) file for (b) (4) (ascorbic acid injection, USP).

We also refer to our June 6, 2011, communication notifying you that we would provide a written response to the questions in your May 20, 2011 meeting request within 60 days after receiving your background materials. The background materials were received on July 22, 2011.

Our responses to your questions are enclosed. If you have additional questions, you must submit a new meeting request.

If you have any questions, call me at (301) 796-5332.

Sincerely,

{See appended electronic signature page}

Pooja Dharia, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure
Written Response

Your questions are repeated below, followed by our responses in **bold** print:

Clinical Strategy

1. Does the Agency concur that a reliance on previous Agency findings of safety and efficacy of the (b) (4) drug product are appropriate for this 505(b)(2) submission as the reference drug product?

   FDA Response: No (b) (4) (b) (4)

2. Does the Agency concur that the literature cited provides the necessary clinical data to support the approval of a proposed indication of treatment of scurvy? ((b) (4))

   FDA Response: The literature provided can form a basis to begin review. It is not possible to determine at this point whether what you have proposed will provide all necessary information. The review team will perform a complete review, including a search for other sources of information.

   We note that two of the three publications provided report studies that were performed in prisoners. When you submit your NDA, part of our review process will include consultation with medical ethicists to 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.

3. Does the Agency concur that the literature cited provides the necessary clinical data to support the approval of a proposed indication of (b) (4)? ((b) (4)

   FDA Response (b) (4)

4. Does the Agency concur that the literature cited provides the necessary clinical data to support the approval of a proposed indication [redacted]?
([redacted])

   FDA Response [redacted]

5. Does the Agency concur that the literature cited provides the necessary clinical data to support the approval of a proposed indication for [redacted]? ([redacted])

   FDA Response: [redacted]

Additional comment regarding the proposed indications:

Please note that at the end of the NDA review process, we may disagree that some [redacted], or we may conclude that they overlap and may in fact be covered by a different nomenclature. Present clearly your argument as to why you consider the [redacted] may not be included in a broader term such as [redacted]

Labeling

6. Does the Agency agree that the content included in [redacted] labeling will be acceptable as a basis for the proposed [redacted] (Ascorbic Acid Injection, USP) labeling?

   FDA Response: Refer to our previous response [redacted]

7. Is the format of the proposed [redacted] (Ascorbic Acid Injection, USP) labeling acceptable?

   FDA Response: We concur with use of the Physician Labeling Rule (PLR) format.

Non-Clinical Overview

8. Does the Agency concur that the data provided in the Nonclinical Overview will support an NDA approval for the proposed indications without further need for Nonclinical data?

FDA Response: The proposed approach of planned submission of published literature supporting nonclinical safety is acceptable. These publications should be submitted with your NDA for review. Further nonclinical studies will not be needed provided the submitted CMC data provides adequate characterization of (b) (4)

Bioavailability

9. Will (b) (4) be appropriate for Ascorbic Acid Injection, USP to satisfy the bioavailability requirements (b) (4) ?

FDA Response: No, (b) (4)

Provided that the information submitted on safety and efficacy is acceptable, and in order to fulfill the requirements for the submission of evidence of in vivo bioavailability or demonstrating the in vivo bioequivalence of your drug product, you may select one of the following options:

a. **Characterize the bioavailability of the Ascorbic Acid Injection, USP**
b. **Determine the relative bioavailability of the Ascorbic Acid Injection, USP to another oral Ascorbic Acid formulation**

CMC - API Vendors

10. Can the Agency provide comment on the applicability of an option to include Ascorbic Acid, USP suppliers in the application whose facilities are registered as food establishments and have not met the drug establishment registration requirements for API manufacturers?

FDA Response: You propose Ascorbic Acid, USP, to be the active pharmaceutical ingredient (API) in a prescription drug to be marketed in the U.S. Therefore, the manufacturer(s) of this API will be subject to FDA pre-approval inspections.

11. In lieu of FDA audit of the API manufacturing site, can the FDA comment on whether audits conducted by EDQM can be relied upon to assure compliance to US GMP (ICH Q7A) with a view of audit information sharing agreements with EDQM and PIC/S?

FDA Response: See the response to question 10.

12. Would inclusion of the applicants (b) (4) the McGuff NDA be acceptable to satisfy the requirements of 21 CFR 314.50(d)(1)(i)?

FDA Response: Your proposal to submit [redacted] complete drug substance documentation (in the NDA or a DMF) will not be acceptable.

As we already stated in the letter dated December 13, 2007, full CMC documentation on the drug substance must be included in the NDA as required by 21 CFR 314.50(d)(1). Reference may be made to a Drug Master File (DMF) for all or part of the required CMC documentation, as allowed by 21 CFR 314.420. If a DMF will be used, the following information should be included in the NDA: Authorized references to the applicable DMFs, a brief section on the general properties of the drug substance, regulatory specifications of the drug substance, retest period, and a list of all manufacturing and testing facilities with a readiness statement for FDA's GMP inspections.

We remind you that, as stated in our letter dated December 13, 2007, adequate comparative information on the [redacted] and [redacted] ascorbic acid will be required in the NDA. This information should cover the structural characterization, physicochemical attributes, and impurity profiles, and should include both data and analysis. The data should include three drug substance batches derived from each source/starting material and the corresponding drug product batches.

For a drug substance derived from [redacted] as you propose for your drug substance, the NDA should include the following information on the source material: [redacted]

CMC – Specification

13. Will the proposed specifications for Ascorbic Acid drug substance meet Agency requirements?

FDA Response: Your proposed drug substance specification complies with the USP monograph with the addition of testing for residual solvents, impurities, endotoxins, and microbial burden, per FDA's December 13, 2007 comments. The limit on the [redacted] should be reduced to [redacted]% (vs. the proposed [redacted]% limit). The limit of [redacted]% for [redacted] will require safety qualification per ICH Q3A "Impurities in New Drug Substances" or [redacted]

CMC-Stability

14. Could the NDA be approved based upon data from a single pilot scale batch manufactured with API sourced from a new API manufacturer and stability data obtained from historical, production scale batches?

    FDA Response: You have not provided sufficient information for us to evaluate in order to respond to your question. The required number of primary stability batches and amount of stability data in support of a new API manufacturer will depend on (1) the differences in the manufacturing processes of the new manufacturer and the other commercial manufacturers listed in the NDA, and (2) the number of primary stability batches and amount of stability data from the other commercial manufacturers listed in the NDA.

15. Is the proposal for a post-approval stability commitment acceptable?

    FDA Response: See the response to question 14.

Pediatric Indication or Waiver

16. Will a waiver from the requirements to conduct pediatric studies be granted based upon the Agencies previous findings of safety and efficacy of ascorbic acid (b) (4)

    FDA Response: This will be a review issue. Under the Pediatric Research Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Your NDA must include (1) a full waiver request, (2) a partial waiver request and a pediatric development plan for the pediatric age groups not covered by the partial waiver request, or (3) a pediatric drug development plan covering the full pediatric age range. All waiver requests must include supporting information and documentation. A pediatric drug development plan must address the all indications proposed in your NDA.

17. If a waiver will not be granted, can (b) (4) '(Ascorbic Acid Injection, USP) drug labeling?

    FDA Response: This will be a review issue. Refer to our previous response concerning (b) (4)

CTD Format

18. Are the noted CTD Sections for the proposed 505(b)(2) application acceptable?

FDA Response: No. Integrated summaries of efficacy and safety will be required.

19. Does the Agency agree [redacted] (b) (4) will be required?

FDA Response: No. [redacted] (b) (4) .

Additional Regulatory Comments Pertaining to Submission of 505(b)(2) Applications:

A 505(b)(2) application would be an acceptable approach at this time based on the information provided.

We recommends tha sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54 and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If there is a listed drug that is the pharmaceutical equivalent to the drug proposed in the 505(b)(2) application, that drug should be identified as the listed drug.

If you choose to rely on FDA's finding of safety and/or effectiveness for a listed drug(s) and you intend to use your proposed comparative clinical trial to establish a bridge between your proposed drug product and the specified listed drug(s), then you should use the specified listed drug(s) (rather than a bioequivalent ANDA product) as the comparator. Note that the listed drug relied upon for approval must have been approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act, not section 505(j) (that is, the listed drug application must be an NDA, not an ANDA).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for a listed drug, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug. You should establish a "bridge" between your proposed drug product and the listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a duplicate of that drug and eligible for approval under section 505(j) of the act, we may refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the

appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

1. In your submission of a 505(b)(2) application, you should clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any of the published literature on which your marketing application relies for approval. If published literature is relied upon, inclusion of copies of the articles would be helpful.

a. In addition to identifying the source of supporting information in your annotated labeling, your marketing application should summarize the information that supports the application in a table similar to the one below.

Source of information (e.g., published literature, name and NDA # of listed drug)	Information provided (e.g., specific sections of the 505(b)(2) application or labeling)
1.	
2.	
3.	
4.	

We remind you that your labeling must conform to the Physicians Labeling Rule (PLR) format and that 505(b)(2) marketing applications are subject to the Prescription Drug User Fee Act.

b. Since we have recommended that you conduct clinical studies to support your application, you should submit a Request for Special Protocol Assessment prior to conducting clinical trials to establish safety and efficacy of your product.

c. We strongly encourage you to request a pre-NDA meeting to be held two to three months prior to your planned submission date.

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/s/

POOJA DHARIA
09/22/2011