CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208609Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # 208609	NDA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: N/A Established/Proper Name: Ephedrine Sulfate, USP Dosage Form: Injection		Applicant: Akorn, Inc. Agent for Applicant (if applicable): Camargo
RPM: Kim Compton		Division: DAAAP

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)	**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: 2/27/17 ***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: 6/15/17	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None CR, 7/15/16
❖ 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): 5
(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:

❖ 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—firm submitted form, claiming no relevant patents ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

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

Action Letters

❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s): 7/15/16 CR, 3/1/17, AP

Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	N/A, no proprietary name proposed
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ None 11/19/15 (SRPI Rvw) DMEPA: ☐ None 2/17/16 and 6/14/16 DMPP/PLT (DRISK): ☒ None OPDP: ☐ None 6/9/16 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	12/19/15 ☐ Not a (b)(2) 2/27/17
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

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

• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: Compared with approved ephedrine sulfate injection products, this application did not propose a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. Does not trigger PREA.	
❖ 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)*	Various
❖ 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)	N/A
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ No mtg
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ 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)*	Firm only held PIND mtg with Agency (PIND 118164); 6/6/2013
❖ 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 7/15/16 (cycle 1); 3/1/17 (cycle 2)
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ None
PMR/PMC Development Templates *(indicate total number)*	☐ None 2/27/17 (5 PMRs)

Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	11/19/15 (filing); 7/5/16
• 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)*	See Clinical Rvw dated 7/5/16, page 9.
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☐ None 4/8/16, OSE/OPE/DPVII Rvw
❖ 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)*	☐ None 11/16/15 (filing); 6/8/16
❖ 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)*	☐ None 11/12/15 (filing); 6/16/16
❖ 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)*	☐ None 7/13/16 (cycle 1); 2/16/17 (cycle 2)
❖ 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)*	(See Cycle 1 Quality Rvw)
☐ 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 Re-evaluation date: 2/28/17 ☐ 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	☒ Done

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/s/

KIMBERLY A COMPTON
03/02/2017

Compton, Kimberly

From: Compton, Kimberly
Sent: Wednesday, February 15, 2017 7:46 PM
To: gbarnette@camargopharma.com
Cc: Compton, Kimberly
Subject: MMA final rule compliance for N 208609, Akorn's ephedrine

Hi Gary,

We refer to Akorn's New Drug Application (NDA) dated and received September 15, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for ephedrine sulfate injection, USP 50mg/mL.

We also refer to your amendments dated December 15, 2016, January 19, and February 3, 2017. These amendments do not comply with 21 CFR 314.60(f), which was added by the final rule on Abbreviated New Drug Applications and 505(b)(2) Applications; Final Rule, 81 FR 69580 (October 6, 2016). The final rule became effective on December 5, 2016.

Section 314.60(f) requires that an amendment to an unapproved 505(b)(2) application contain an appropriate patent certification or statement described in 21 CFR 314.50(i), or a "recertification" for a previously submitted paragraph IV certification, if approval is sought for changes described in any of the following types of amendments:

- To add a new indication or other condition of use;
- To add a new strength;
- To make other than minor changes in product formulation; or
- To change the physical form or crystalline structure of the active ingredient.

If an amendment to the 505(b)(2) application does not contain a patent certification (or recertification) or statement, the applicant must verify that the proposed change described in the amendment is not one of the types of amendments described above.

We recommend that the cover letter for your response to this information request and for future amendments to your unapproved 505(b)(2) application either:

1) states that the amendment contains a patent certification (or recertification) or statement required by 21 CFR 314.60(f)(1); or

2) verifies that the proposed change described in the amendment is not one of the types of amendments described in 21 CFR 314.60(f)(1), as appropriate.

Your response to this information request must clearly reference your amendments dated December 15, 2016, January 19, and February 3, 2017.

If you have any questions, contact me for follow up.

Thank you,
Kim Compton

Sr. Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
301-796-1191

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/s/

KIMBERLY A COMPTON
02/15/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208609

ACKNOWLEDGE –
CLASS 2 RESUBMISSION

Akorn Inc.
c/o Camargo Pharmaceuticals Services, LLC
2505 Meridian Parkway, Suite 175
Durham, NC 27713

Attention: K. Gary Barnette, PhD
Vice President, Drug Development

Dear Dr. Barnette:

We acknowledge receipt on December 15, 2016, of your December 15, 2016, resubmission to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for ephedrine sulfate injection, USP 50 mg/mL

We consider this a complete, class 2 response to our July 15, 2016, action letter. Therefore, the user fee goal date is June 15, 2017.

If you have any questions, call me at (301) 301-796-1191

Sincerely,

{See appended electronic signature page}

Kimberly A. Compton, RPh
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

KIMBERLY A COMPTON
12/22/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208609

NDA ACKNOWLEDGMENT

Akorn Inc.
c/o Camargo Pharmaceuticals Services, LLC
2505 Meridian Parkway, Suite 175
Durham, NC 27713

Attention: K. Gary Barnette, PhD
Vice President, Drug Development

Dear Dr. Barnette:

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: Ephedrine Sulfate Injection, USP 50mg/mL

Date of Application: September 15, 2015

Date of Receipt: September 15, 2015

Our Reference Number: NDA 208609

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 14, 2015, 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).

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 Anesthesia, Analgesia, and Addiction 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) 796-1191.

Sincerely,

{See appended electronic signature page}

Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

EVA L YUAN
11/02/2015

From: Sullivan, Matthew
To: "Barnette. Gary"
Cc: Compton, Kimberly
Subject: Caron/container label for NDA 208609
Date: Wednesday, June 08, 2016 3:34:00 PM

Hi Gary –

Kim is out this week, so I'm passing along this request to you.

After reviewing your revised container label and carton labeling submitted on June 3, 2016, we have the following comment:

(b) (4)

When revising the route of administration statement on the principal display panel, we recommend the statement "For Intravenous Use". The use (b) (4) *has been reported in postmarketing error cases and is discouraged by the Institute of Safe Medication Practices (ISMP).*

Please revise and resubmit to your NDA.

Please let me know if you have any questions,

Thanks,
Matt

Matthew W. Sullivan, M.S.
Supervisory Regulatory Health Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9723
matthew.sullivan@fda.hhs.gov

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/s/

MATTHEW W SULLIVAN
06/08/2016

Compton, Kimberly

From: Compton, Kimberly
Sent: Friday, May 06, 2016 4:21 PM
To: Barnette. Gary
Cc: Compton, Kimberly
Subject: Requests for N 208609

Hi Gary,

We are continuing to review the Akorn NDA and the CMC folks have the following request:

1. Revise your label to include directions in the Dosage and Administration section for dilution of the drug product for administration. You can submit revised labeling in WORD format only during this phase of the review.

2. Provide data to support the stability of the diluted drug product in the diluents specified in the label. This information should be included in section 3.2.P.2.6. See the guidance for industry *M4Q: The CTD — Quality*, available at, http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073280.pdf. Resubmit section 3.2.P.2 following the format in this Guidance.

Please let us know if you have any questions on our requests.

Just FYI, I will be out of the office Mon-Wed May 9-11, so if you need immediate assistance during that time, please contact my supervisor, Matt Sullivan (matthew.sullivan@fda.hhs.gov).

Thanks!
Kim

Kimberly Compton
Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
301-796-1191

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/s/

KIMBERLY A COMPTON
05/06/2016

Compton, Kimberly

From: Compton, Kimberly
Sent: Saturday, January 16, 2016 1:30 AM
To: 'Barnette. Gary'
Cc: Norris, Kristi
Subject: RE: Info reqest for Akorn's N 208609

Hi Gary,

I spoke to the team and they asked me to convey that they would in fact like Akorn to prepare the responses for safety as requested originally requested, however, instead of a summary of the efforts/results at contacting the original authors, we request specifics of the attempts and results with as much detail as possible. What might work well is a table listing the articles with a column describing who was contacted/spoke with (actual person's name and their position, if they were not a primary author), as well as the details of the conversation and the information that was provided from the attempt.

Please let me know if you have any questions on our request.

Thanks
Kim

From: Barnette. Gary [mailto:gbarnette@camargopharma.com]
Sent: Thursday, January 14, 2016 9:40 AM
To: Compton, Kimberly
Cc: Norris, Kristi
Subject: RE: Info reqest for Akorn's N 208609

Hello Kim,

Hope you are doing well in 2016!

Unfortunately, the information on the form of ephedrine used in the efficacy papers was just not reported and yes, the table contains what was reported in the publication. As we talked about in the PIND meeting and at the request of FDA, we sent communications to the primary authors of the papers and were not able to get any information on the form of ephedrine. As FDA and we predicted in the PIND meeting, most of the communications were returned to sender and the very few that we received back did not have any information on formulation due to age of the study or some other reason. But we made the effort. We will provide a summary of our efforts in these communications as you requested below.

As I mentioned above, we are happy to provide a similar table for the safety papers, but the formulation column will be essentially the same as the efficacy paper table.

How would you like us to proceed?

Thanks

Gary

K. Gary Barnette, Ph.D.
Vice President of Drug Development

THE GLOBAL 505(B)(2) EXPERTS
Camargo
PHARMACEUTICAL SERVICES

Cincinnati, OH ● Durham, NC

513-618-0367 (office)
(b) (6)

Biotech Showcase 2016
January 11-13, 2016
San Francisco, CA

From: Compton, Kimberly [mailto:Kimberly.Compton@fda.hhs.gov]
Sent: Wednesday, January 13, 2016 2:51 PM
To: Barnette. Gary <gbarnette@camargopharma.com>
Cc: Norris, Kristi <knorris@camargopharma.com>
Subject: RE: Info reqest for Akorn's N 208609

Hi Gary,

Thank you for the submission addressing our question about which form of ephedrine was used in the studies submitted to support efficacy for N 208609; we now require the same information about studies submitted to support the *safety* of ephedrine for the NDA.

However, we note that you stated information on the form of ephedrine used in the studies was not specified. Please clarify, both as it relates to your 1/6/16 submission and for your response to the above, if you are reporting what is found in the papers, or whether you actually reached out to the authors to obtain this information.

Please provide the documentation describing the extent and methods that you utilize in your attempt to obtain the above information (for safety and efficacy).

Thanks
Kim

From: Barnette. Gary [mailto:gbarnette@camargopharma.com]
Sent: Wednesday, December 23, 2015 3:10 PM
To: Compton, Kimberly
Cc: Norris, Kristi
Subject: RE: Info reqest for Akorn's N 208609

Thanks Kim, We will work on this and get this information back to you, but it will be after the first of the year as some of my team members are out for the holidays. Is this acceptable?

I hope you have a wonderful Christmas and New Year.

Thanks

Gary

K. Gary Barnette, Ph.D.
Vice President of Drug Development

THE GLOBAL 505(B)(2) EXPERTS
Camargo
PHARMACEUTICAL SERVICES

Cincinnati, OH ● Durham, NC

513-618-0367 (office)
(b) (6)

Biotech Showcase 2016
January 11-13, 2016
San Francisco, CA

From: Compton, Kimberly [mailto:Kimberly.Compton@fda.hhs.gov]
Sent: Wednesday, December 23, 2015 3:03 PM
To: Barnette. Gary <gbarnette@camargopharma.com>
Subject: Info reqest for Akorn's N 208609

Hi Gary,

We have an information request for this NDA (208609) from the review team:

Provide information on whether the ephedrine used in each of the articles supporting efficacy is USP ephedrine. If no information on USP exists, please identify the manufacturer of ephedrine used in each article that you are using to support efficacy.

Please let me know if you have any questions about our request.

Thanks and Happy Holidays,
Kim

Kimberly Compton
Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
301-796-1191

From: Compton, Kimberly
Sent: Thursday, November 19, 2015 9:34 PM
To: gbarnette@camargopharma.com
Subject: 74 day letter for Akorn's N 208609

Hi Gary,

Attached please find an e-copy of the 74 day letter for N 208609 for Akorn.
<< File: N 208-609 Filing Issues ltr FINAL.pdf >>
Thanks
Kim

Kimberly Compton
Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
301-796-1191

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/s/

KIMBERLY A COMPTON
01/25/2016

Compton, Kimberly

From: Compton, Kimberly
Sent: Saturday, January 16, 2016 1:24 AM
To: 'Barnette. Gary'
Cc: Compton, Kimberly
Subject: Info reqest for Akorn's N 208609

HI Gary,

The Maternal Health Team asked us to forward the following information request for N 208609 (Ephedrine):

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.

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

Submit the following information by January 30, 2016

- a review and summary of all available published literature regarding ephedrine use in pregnant and lactating women
- a review and summary of relevant cases reported in your pharmacovigilance database
- an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry (if applicable)
- a revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR.

Refer to the guidance for industry, *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf.

Please let me know if you have any questions about this request.

Thanks
Kim

Kimberly Compton
Kimberly Compton, R.Ph.

Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
301-796-1191
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KIMBERLY A COMPTON
01/25/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208609

FILING COMMUNICATION –
FILING REVIEW ISSUES IDENTIFIED

Akorn Inc.
c/o Camargo Pharmaceuticals Services, LLC
2505 Meridian Parkway, Suite 175
Durham, NC 27713

Attention: K. Gary Barnette, PhD
Vice President, Drug Development

Dear Dr. Barnette:

Please refer to your New Drug Application (NDA) dated and received on September 15, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Ephedrine Sulfate Injection, USP 50mg/mL.

We also refer to your amendment dated October 26, 2015.

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 15, 2016.

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 17, 2016.

We are not currently planning to hold an advisory committee meeting to discuss this application.

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

Nonclinical
We note that your drug substance specifications (b) (4) and drug product stability specification (b) (4) exceed ICH

thresholds. Also, you have neither provided adequate justifications for the safety of these specifications nor have you completed the required toxicology studies outlined in the PreIND meeting minutes. Your safety justification based on LD_{50} data to justify the specification (b) (4) is not adequate. You must either tighten these specifications to comply with ICH or qualify (b) (4).

As we have previously stated, for the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per ICH Q3A(R2) and ICH Q3B(R2). In order to provide adequate qualification:

a. You must complete a minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.

b. In addition, you must conduct a repeat-dose toxicology study of appropriate duration to support the proposed indication. In this case, a study of 14-days duration should be completed.

Refer to:
Guidance for industry, *Q3A(R2) Impurities in New Drug Substances*
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073385.pdf

and

Guidance for industry, *Q3B(R2) Impurities in New Drug Products*
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073389.pdf

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

Additionally, we request that you submit the following information:

1. A single and consistent set of specifications for release of the Drug Substance that are the same as or tighter than (b) (4) specifications.

2. A single consistent set of specifications for release and stability of the Drug Product.

3. Justification supporting your proposal to have a different set of impurity specifications at release and for stability studies.

4. Include a test for osmolality as part of the release testing of the drug product. Propose a specification for osmolality and provide supportive data.

5. Include a determination of optical rotation, not just an ID test confirming levorotary, in the drug product testing. Further, include any impurities in the drug substance that are identified as potential degradants in the impurity profile for drug product release. Provide batch data for impurity testing according to the proposed specifications in Section 3.2.P.5.1.

ADDITIONAL COMMENTS REGARDING MARKETED UNAPPROVED PRODUCTS

The Agency encourages firms to voluntarily comply with the law by submitting applications for previously marketed unapproved new drugs. This process benefits public health by increasing assurance that marketed drugs are safe and effective for their intended uses as well as manufactured consistent with current good manufacturing practice. When a company obtains approval for which other companies market unapproved versions, the FDA is more likely to consider a compliance action. However, FDA considers several factors such as the effect on public health of proceeding immediately to remove the unapproved products from the market, the ability of the applicant holder to meet patient needs by supplying the entire market, assuring that the components and finished drug products are manufactured under quality standards, and efficient use of Agency resources. We encourage your firm to consider these important factors as the application progresses through the review process and to open discussions with the Drug Shortage Staff when appropriate. We refer you to the Agency website which provides additional guidance on the compliance actions for marketed unapproved products, http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/SelectedEnforcementActionsonUnapprovedDrugs/default.htm

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *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 42 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.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

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. Please adjust the margins on all sides so they are at least ½ inch as required.

2. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI. The line in your document appears at the top of the FPI page, but is typically included at the bottom of the TOC page. Please include it at the bottom of the TOC page or justify why this is not possible.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by December 18, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

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). 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) 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.

(b) (4)

If you have any questions, call Kimberly Compton, Senior Regulatory Project Manager, at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

SHARON H HERTZ
11/19/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 118164

MEETING MINUTES

Camargo Pharmaceutical Services, LLC
9825 Kenwood Road, Suite 203
Cincinnati, OH 45242-6252

Attention: K. Gary Barnette, Ph.D.
Vice President, Drug Development

Dear Dr. Barnette:

Please refer to your Pre-Investigational New Drug Application (PIND) file for ephedrine sulfate.

We also refer to the meeting between representatives of your firm and the FDA on June 6, 2013. The purpose of the meeting was to discuss the development program for ephedrine sulfate (b) (4)

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact me at (301) 796-9380.

Sincerely,

{See appended electronic signature page}

Ayanna Augustus, Ph.D., R.A.C.
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

Reference ID: 4069861

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-IND

Meeting Date and Time: June 6, 2013; 12:00 PM
Meeting Location: White Oak, Bldg 22, Room 1309

Application Number: 118164
Product Name: Ephedrine sulfate
Indication: (b) (4)

Sponsor/Applicant Name: Camargo Pharmaceutical Services, LLC
Meeting Chair: Christopher Breder, M.D., Ph.D., Clinical Team Leader
Meeting Recorder: Ayanna Augustus, Ph.D., R.A.C.

FDA Attendees	Title
Bob A. Rappaport, M.D.	Director
Rigoberto Roca, M.D.	Deputy Division Director
Jin Chen, M.D., Ph.D., M.P.H.	Clinical Reviewer
Christopher Breder, M.D. Ph.D.	Clinical Team Leader
Dan Mellon, Ph.D.	Pharmacology/Toxicology Supervisor
Olen Stephens, Ph.D.	CMC Lead, ONDQA
David Lee, Ph.D.	Clinical Pharmacology Reviewer
Yun Xu, Ph.D.	Clinical Pharmacology Team Leader
Ayanna Augustus, Ph.D., R.A.C.	Regulatory Health Project Manager
Barbara Wesley, M.D.	Clinical Reviewer, Division of Bone, Reproductive and Urologic Products (DBRUP)
Christina Chang, M.D., M.P.H.	Acting Clinical Team Leader, DBRUP
Sponsor Attendees	**Title**
K. Gary Barnette, Ph.D.	Vice President, Drug Development, Camargo Pharmaceutical Services, LLC
Josh Johnson, Ph.D.	Research Scientist, Camargo Pharmaceutical Services, LLC

20 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

AYANNA S AUGUSTUS
06/25/2013

Reference ID: 4069861