

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207534Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 207534

SUPPL #

HFD #

Trade Name Symjepi

Generic Name Epinephrine

Applicant Name Adamis

Approval Date, If Known June 15, 2017

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(2)

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

YES ☐ NO ☒

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

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

c) Did the applicant request exclusivity?

YES ☐ NO ☒

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

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

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

NDA #(s).

NDA# 204200 and 204640 Adrenalin (epinephrine injection)

NDA# 20800 Twinject (epinephrine injection)

NDA# 201739 Auvi-Q

NDA# 19430 Epipen

2. Combination product.

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

YES ☐ NO ☒

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

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

YES ☐ NO ☐

If yes, explain:

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

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

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

- b) For each investigation identified as "essential to the approval", does the investigation

duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

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

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

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

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

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

Investigation #1

YES ☐

Explain:

!

!

! NO ☐

! Explain:

Investigation #2

YES ☐

Explain:

!

!

! NO ☐

! Explain:

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

YES ☐

NO ☐

If yes, explain:

=====

Name of person completing form:

Title: Senior Regulatory Health Project Manager

Date: June 1, 2017

Name of Deputy Division Director signing form: Lydia Gilbert-McClain, M.D.

Title: Deputy Division Director, Division of Pulmonary, Allergy, and Rheumatology Products.

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

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

/s/

COLETTE C JACKSON
06/15/2017

LYDIA I GILBERT MCCLAIN
06/15/2017

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 207534 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Symjepi Established/Proper Name: Epinephrine Dosage Form: Injection		Applicant: Adamis Agent for Applicant (if applicable):
RPM: Colette Jackson		Division: DPARP
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)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> - Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. - Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☐ No changes ☒ New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: June 1, 2017 <i>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.</i>
❖ Actions		
- Proposed action - User Fee Goal Date is <u>June 15, 2017</u>		☒ AP ☐ TA ☐ CR
Previous actions <i>(specify type and date for each action taken)</i>		☐ None June 3, 2016, and March 27, 2015
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		☐ Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

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

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

(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

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

BLAs: Subpart E

- ☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)

Subpart H

- ☐ Approval based on animal studies

- 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)?	☒ No ☐ Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Actions and dates: CR June 3, 2016, and CR March 27, 2015
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	☒ Included
Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	☐ Medication Guide ☐ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	☒ Included
Original applicant-proposed labeling	☒ Included
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
Most-recent draft labeling	☒ Included
❖ Proprietary Name - Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> - Review(s) <i>(indicate date(s))</i>	PNR Conditionally Acceptable February 8, 2017, May 6, 2016, and March 2, 2015 January 31, 2017, May 6, 2016, and February 27, 2015
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: ☐ None 8/16/2014 DMEPA: ☐ None 2/2/2015, 5/24/2016, and 4/10/2017 DMPP/PLT (DRISK): ☐ None 2/26/2015, 5/25/2016, and 5/12/2017 OPDP: ☐ None 2/26/2015, 6/2/2016, and 4/28/2017 SEALD: ☒ None CSS: ☒ None Product Quality ☐ None 4/19/2017 Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	8/1/2014
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☐ Not a (b)(2) 3/9/2015, 5/8/2016, and 3/21/2017
❖ NDAs/NDA supplements only: Exclusivity Summary <i>(signed by Division Director)</i>	☒ Completed (Do not include)

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

❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) • Date reviewed by PerC _____ If PerC review not necessary, explain: Does not trigger PREA (does not include a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration)	
❖ 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) (<i>include only the completed template(s) and not the meeting minutes</i>)	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) (<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)	
❖ 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.) (<i>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</i>)	June 6, and 16, August 6, and November 21, 2014, and January 9, and February 27, 2015, and January 13, February 22, March 3, 16, and 24, April 21, and 25, and May 6, and December 23, 2016, and February 9 (2), and 24, March 22, and May 19, and 31, 2017
❖ 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 (<i>indicate date of mtg</i>)	☐ N/A or no mtg August 5, 2015
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☒ No mtg
• EOP2 meeting (<i>indicate date of mtg</i>)	☒ No mtg
• Mid-cycle Communication (<i>indicate date of mtg</i>)	☒ N/A
• Late-cycle Meeting (<i>indicate date of mtg</i>)	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)	

❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ None
Division Director Summary Review (<i>indicate date for each review</i>)	☐ None June 15, 2017, and June 3, 2016, and March 27, 2015
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☐ None June 1, 2017, and May 20, 2016, and March 6, 2015
PMR/PMC Development Templates (<i>indicate total number</i>)	☐ None 1
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
• Clinical review(s) (<i>indicate date for each review</i>)	July 14, and August 28, 2014, and February 18, 2015, and May 9, 2016, and May 22, 2017
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ 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 (<i>indicate date of review/memo</i>)	August 28, 2014
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ N/A
❖ Risk Management - REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) - REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) - Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	☒ None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	☐ No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	☐ No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	☐ No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	☐ None

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).

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	☒ No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	☒ No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	☐ None July 13, 2014, and February 26, 2015
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	☒ No separate review
• Supervisory Review(s) <i>(indicate date for each review)</i>	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	☐ None June 25, 2014, and February 18, 2015, and April 20, and May 3, 2017
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	☒ None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review <i>(indicate date for each review)</i>	☒ None
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i>	☐ None June 23, and 24, July 15, November 5, 2014, and January 5, and 16, February 23, 2015, and May 5, 2016, and April 19, 2017 (2)
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	☐ None CDRH reviews June 26 (2), and December 12, 2014, and April 21, May 20, and June 2, 2016 and June 9, 2017. P/T consult review dated October 27, 2014.
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	February 23, 2015 and May 5, 2016, CMC reviews
☐ Review & FONSI <i>(indicate date of review)</i>	
☐ Review & Environmental Impact Statement <i>(indicate date of each review)</i>	

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

❖ 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) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	☒ Acceptable ☐ Withhold recommendation ☐ Not applicable

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 <i>(Notify CDER OND IO)</i>
Finalize 505(b)(2) assessment	☒ Done
❖ For Breakthrough Therapy (BT) Designated drugs: Notify the CDER BT Program Manager	☐ Done <i>(Send email to CDER OND IO)</i>
❖ 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 <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	☒ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	
❖ Take Action Package (if in paper) down to Document Room for scanning within two business days	

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

/s/

COLETTE C JACKSON
06/15/2017



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

DATE: June 6, 2017

To: Dennis J. Carlo	From: Colette Jackson
Company: Adamis Pharmaceuticals Corp	Division of Pulmonary, Allergy, and Rheumatology Products
Email Address: dcarlo@adamispharma.com	Fax number: 301-796-9718
Phone number: 858-412-7943	Phone number: 301-796-1230
Subject: NDA 207534 Epinephrine Injection- FDA Proposed Labeling	

**Total no. of pages including
cover:**

Comments:

Document to be mailed:	YES	xNO
-------------------------------	------------	------------

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 207534
Adamis Pharmaceuticals Corporation
Epinephrine Injection USP (b) (4)

We refer to your December 15, 2016, NDA resubmission for Epinephrine Injection. We also refer to the labeling submitted in your June 2, 2017, submission. We are providing FDA recommendations and comments in the attached labeling for the proposed Patient Information and Instructions for Use. The FDA-proposed insertions are underlined and deletions are in strike-out. Our comments and recommendations are not all-inclusive and additional comments may be forthcoming.

Please provide a response to the request by email (Colette.Jackson@fda.hhs.gov) by COB Friday, June 9, 2017. Your response must also be submitted formally to your NDA application shortly thereafter. If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Enclosures: FDA Proposed Labeling (annotated and unannotated)

18 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS)
immediately following this page

Drafted: Colette Jackson/June 6, 2017

Initialed: Peter Starke/ June 5, 2017
Lydia Gilbert-McClain/ June 5, 2017

Finalized: CCJ/ June 6, 2017

Filename: 207534 Label fax June 2017.doc

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

/s/

COLETTE C JACKSON
06/06/2017



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

DATE: May 31, 2017

To: Dennis J. Carlo	From: Colette Jackson
Company: Adamis Pharmaceuticals Corp	Division of Pulmonary, Allergy, and Rheumatology Products
Email Address: dcarlo@adamispharma.com	Fax number: 301-796-9718
Phone number: 858-412-7943	Phone number: 301-796-1230
Subject: NDA 207534 Epinephrine Injection- FDA Information Request	

Total no. of pages including cover:

Comments:

Document to be mailed:	YES	xNO
-------------------------------	------------	------------

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 207534
Adamis Pharmaceuticals Corporation
Epinephrine Injection USP (b) (4)

We refer to your December 15, 2016, NDA resubmission for Epinephrine Injection. We also refer to your submission dated April 28, 2017. We have the following request.

Provide your agreement to conduct the following post-marketing commitment (PMC) and agreement to the final report submission date listed below.

PMC #1: Provide an updated Fault Tree Analysis, specifically for Less Than Full Dose Delivered that includes the probability data for each identified basic failure mode and show that the quantification of the fault tree analysis supports the device reliability specification, 99 .99%. The data could include manufacturing controls (i.e. in process controls and release testing) or probability data from design verification tests

Final Report Submission: August 15, 2017

Please provide a response to the request by email (Colette.Jackson@fda.hhs.gov) by COB Friday, June 2, 2017. Your response must also be submitted formally to your NDA application shortly thereafter. If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Drafted: Colette Jackson/May 31, 2017

Initialed: Sandy Barnes/ May 31, 2017
Sally Seymour/ May 31, 2017

Finalized: CCJ/ May 31, 2017

Filename: 207534 PMC fax May 2017.doc

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

/s/

COLETTE C JACKSON
05/31/2017



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II**

ELECTRONIC CORRESPONDENCE

DATE: May 19, 2017

To: Dennis J. Carlo	From: Colette Jackson
Company: Adamis Pharmaceuticals Corp	Division of Pulmonary, Allergy, and Rheumatology Products
Email Address: dcarlo@adamispharma.com	Fax number: 301-796-9718
Phone number: 858-412-7943	Phone number: 301-796-1230
Subject: NDA 207534 Epinephrine Injection- FDA Proposed Labeling	

**Total no. of pages including
cover:**

Comments:

Document to be mailed:	YES	xNO
-------------------------------	------------	------------

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 207534
Adamis Pharmaceuticals Corporation
Epinephrine Injection USP (b) (4)

We refer to your December 15, 2016, NDA resubmission for Epinephrine Injection. We also refer to the labeling submitted in your February 8, March 14, and April 28, 2017, submissions. We are providing FDA recommendations and comments in the attached labeling for the proposed Package Insert, Patient Information, and Instructions for Use. The FDA-proposed insertions are underlined and deletions are in strike-out. Our comments and recommendations are not all-inclusive and additional comments may be forthcoming. We also have the following comments regarding your device and carton labeling.

1. Provide revised text for the prefilled syringe label with Manufacturer / Distributor name included [See 21 CFR 201.10(i)].
2. Provide revised text for Carton Labels for both Single pack and Two Pack that includes names of all inactive ingredients and quantitative ingredient information, which is required for injectable products [See 21 CFR 201.10(a), 21 CFR 201.100(b)(5)(iii)] on the outer package, when it was not possible to include such complete composition information on the primary container [See 21 CFR 201.10(i)].

Please provide a response to the request by email (Colette.Jackson@fda.hhs.gov) by COB Monday, May 29, 2017. Your response must also be submitted formally to your NDA application shortly thereafter. If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Enclosures: FDA Proposed Labeling (annotated and unannotated)

37 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

Drafted: Colette Jackson/May 19, 2017

Initialed: Peter Starke/ May 17, 2017
Lydia Gilbert-McClain/ May 17, 2017
Craig Bertha/ May 4, 2017
Venkateswara Pavuluri/May 4, 2017
Julia Pinto/ May 4, 2017

Finalized: CCJ/ May 19, 2017

Filename: 207534 Label fax May 2017.doc

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

/s/

COLETTE C JACKSON
05/19/2017



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II**

ELECTRONIC CORRESPONDENCE

DATE: May 19, 2017

To: Dennis J. Carlo	From: Colette Jackson
Company: Adamis Pharmaceuticals Corp	Division of Pulmonary, Allergy, and Rheumatology Products
Email Address: dcarlo@adamispharma.com	Fax number: 301-796-9718
Phone number: 858-412-7943	Phone number: 301-796-1230
Subject: NDA 207534 Epinephrine Injection- FDA Information Request	

Total no. of pages including cover: 3

Comments:

Document to be mailed:	YES	xNO
-------------------------------	------------	------------

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 207534
Adamis Pharmaceuticals Corporation
Epinephrine Injection USP (b) (4)

We refer to your December 15, 2016, NDA resubmission for Epinephrine Injection. We also refer to your April 28, 2017, submission. We have the following comment and request for information.

As discussed during our teleconference on May 17, 2017, the fault tree analysis for Less Than Full Dose Delivered is incomplete because it does not include the probability data to support the reliability specification. Provide an updated fault tree analysis specifically for Less than Full Dose Delivered that includes the probability data for each identified basic failure mode and show that the quantification of the fault tree analysis supports the device reliability specification. The data could include manufacturing controls (i.e., in-process controls and release testing) or probability data from design verification tests.

In order to facilitate our review, we ask you provide a response by COB May 24, 2017, by email at Colette.Jackson@FDA.HHS.GOV followed by an official submission to the application. If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Drafted: Colette Jackson/May 17, 2017

Initialed: CDRH Alan Stevens and John McMichael/ May 17, 2017
Lydia Gilbert-McClain/ May 17, 2017

Finalized: CCJ/ May 17, 2017

Filename: 207534 CDRH fax May 2017.doc

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

/s/

COLETTE C JACKSON
05/19/2017



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

DATE: March 22, 2017

To: Dennis J. Carlo	From: Colette Jackson
Company: Adamis Pharmaceuticals Corp	Division of Pulmonary, Allergy, and Rheumatology Products
Email Address: dcarlo@adamispharma.com	Fax number: 301-796-9718
Phone number: 858-412-7943	Phone number: 301-796-1230
Subject: NDA 207534 Epinephrine Injection- FDA Information Request	

Total no. of pages including cover: 3

Comments:

Document to be mailed:	YES	xNO
-------------------------------	------------	------------

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 207534
Adamis Pharmaceuticals Corporation
Epinephrine Injection USP (b) (4)

We refer to your December 15, 2016, NDA resubmission for Epinephrine Injection which included a human factors report. We have the following comments.

1. In your human factors report under 8.8.8.1 Task 1: Open case, five participants said that it was difficult to find the latch. Additionally, five participants initially pulled from other areas on the box to open the case, including the middle, long side, and the opposite side from latch. You state as a root cause that participants reported they did not see the label “pull latch to open,” and did not see the arrow on the box because it was only embossed rather than colored. Some participants said they did not see the latch because it blended in with the case. Given that your product is intended to be used in an emergency setting, the product design should be optimized to allow users to recognize quickly where they need to open the case. We ask that you consider further optimizing the information on the case to call out the user’s attention as to where they need to pull the latch to open the case. For example, you may consider labeling changes that may make the latch more quickly recognizable (i.e. an arrow on the yellow label pointing down to the latch or other options) to the user.
2. Under 8.8.8.4 Task 4: Insert in thigh/location of injection under root cause one root cause listed was that some participants thought the images on the device labels showing the recommended injection location looked like another area of the body other than the thigh. We note that the image on the device label differs from the image contained in the IFU. We recommend that you further optimize the image to minimize user confusion. For example, you may consider using the same image that you use in the IFU.

In order to facilitate our review, we ask you provide a response by COB March 28, 2017, by email at Colette.Jackson@FDA.HHS.GOV followed by an official submission to the application. If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Drafted: Colette Jackson/March 21, 2017

Initialed: Sandy Barnes/ March 21, 2017
DMEPA/ March 16, and 21, 2017

Finalized: CCJ/ March 22, 2017

Filename: 207534 DMEPA fax March 2017.doc

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

/s/

COLETTE C JACKSON
03/22/2017



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

DATE: February 24, 2017

To: Dennis J. Carlo	From: Colette Jackson
Company: Adamis Pharmaceuticals Corp	Division of Pulmonary, Allergy, and Rheumatology Products
Email Address: dcarlo@adamispharma.com	Fax number: 301-796-9718
Phone number: 858-412-7943	Phone number: 301-796-1230
Subject: NDA 207534 Epinephrine Injection- FDA Information Request	

Total no. of pages including cover: 4

Comments:

Document to be mailed:	YES	xNO
-------------------------------	------------	------------

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 207534
Adamis Pharmaceuticals Corporation
Epinephrine Injection USP (b) (4)

We refer to your December 15, 2016, NDA resubmission for Epinephrine Injection. We also refer to your February 17, 2017, submission which was in response to our February 9, 2017, information request. We believe there is sufficient time within this review cycle for the following information to be submitted and reviewed prior to action.

1. The sharps injury prevention test report requires FDA review prior to marketing the proposed combination product in NDA 207534 to assess the safety of the redesigned combination product device parts. The FDA Guidance document for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features on how to complete the testing recommends using a sample size of 500 with zero failures to demonstrate an adequate confidence limit. Please provide the complete sharps injury prevention test report and review the following guidance document prior to completing the testing. (*Guidance for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features*.
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071663.htm>)
2. The biocompatibility test reports require FDA review prior to marketing the proposed combination product in NDA 207534 to assess the safety of the redesigned combination product device parts. Please provide the following biocompatibility test protocols and test reports based on ISO 10993-1 on all patient-contacting components on the final finished device constituent parts.
 - a) *In vitro* cytotoxicity testing based on ISO 10993 Biological evaluation of medical devices, Part 5 Test for *in vitro* cytotoxicity;
 - b) Irritation testing based on ISO 10993 Biological evaluation of medical devices, Part 10 Tests for irritation and skin sensitization;
 - c) Delayed hypersensitivity testing based on ISO 10993 Biological evaluation of medical devices, Part 10 Tests for irritation and skin sensitization.

Please review the following guidance document prior to completing the testing:
Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"
<https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm348890.pdf>

3. You have not addressed the concerns relating to the reliability of the device as outlined in the Complete Response letter 'Additional Comments'. These

concerns remain valid and a response is expected prior to marketing the proposed combination product in NDA 207534. Please address the following:

In your submission dated May 5, 2016, your response to question 2 regarding reliability, you state the redesigned Epinephrine Injection device, as presently submitted, underwent reliability testing with the intent to establish reasonable reliability of the device, and its ability to meet performance requirements throughout an 18-month expiratory period. You provided the following primary reliability requirement:

The device shall be capable of delivering 0.30 mL +/- (b) (4) % of drug over the 18- month expected use life with a (b) (4) % reliability and (b) (4) % confidence level. The file does not provide a justification supporting the validity of this reliability specification to adequately mitigate risk of failure.

It is unclear how you are achieving the reliability specification with testing that has been provided. As previously requested, the testing should be based on a risk assessment that determines the potential initiating events that could result in failure. Based on your analysis, the testing program should verify that the reliability specification has been satisfied. For example, it appears that you are (b) (4)

Please provide the following information:

- a. Provide a justification for the reliability and confidence interval specification.
- b. Provide the risk analysis (e.g., fault tree) used to identify the initiating events.
- c. Identify the sample size needed to meet the specification. We recommend defining success and failure for each trial and using the binomial distribution to determine the necessary sample size to meet the reliability and confidence interval requirements.
- d. Provide the test protocols and data demonstrating that the samples, which are sequentially exposed to the preconditioning steps, meet the success criteria.

In order to facilitate our review, we ask you provide a response by COB April 14, 2017, by email at Colette.Jackson@FDA.HHS.GOV followed by an official submission to the application. If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Drafted: Colette Jackson/February 23, 2017

Initialed: Sandy Barnes/ February 24, 2017
Kathleen Fitzgerald/ February 23, 2017
Alan Stevens/ February 23, 2017

Finalized: CCJ/ February 24, 2017

Filename: 207534 CDRH ODE fax no 2 February 2017.doc

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

/s/

COLETTE C JACKSON
02/24/2017



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

DATE: February 9, 2017

To: Dennis J. Carlo	From: Colette Jackson
Company: Adamis Pharmaceuticals Corp	Division of Pulmonary, Allergy, and Rheumatology Products
Email Address: dcarlo@adamispharma.com	Fax number: 301-796-9718
Phone number: 858-412-7943	Phone number: 301-796-1230
Subject: NDA 207534 Epinephrine Injection- FDA Information Request	

Total no. of pages including cover: 3

Comments:

Document to be mailed:	YES	xNO
-------------------------------	------------	------------

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 207534
Adamis Pharmaceuticals Corporation
Epinephrine Injection USP (b) (4)

We refer to your December 15, 2016, NDA resubmission for Epinephrine Injection. We have the following comments and requests for information.

In your cover letter, it states:

1.2. Other Comments

In addition to the deficiency identified FDA had comments regarding the reliability, sharps injury prevention failure rate, and biocompatibility tests conducted for the Symjepi product. As agreed upon by FDA in the Preliminary Meeting Comments, Adamis will submit responses to the additional comments by FDA as a separate submission sequence after this resubmission, and after the start of the new review cycle.

Please clarify when this information will be provided. In addition, provide the complete performance test reports for the revised Epinephrine Injection design verification and validation. The resubmission contained only summaries of the test reports.

In order to facilitate our review, we ask you provide a response by COB February 13, 2017, by email at Colette.Jackson@FDA.HHS.GOV followed by an official submission to the application. If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Drafted: Colette Jackson/February 9, 2017

Initialed: Kathleen Fitzgerald/ February 8, 2017

Finalized: CCJ/ February 9, 2017

Filename: 207534 CDRH ODE fax February 2017.doc

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

/s/

COLETTE C JACKSON
02/09/2017



NDA 207534

MEETING MINUTES

Adamis Pharmaceuticals Corporation
11682 El Camino Real, Suite 100
San Diego, CA 92130

Attention: Dennis J. Carlo, Ph.D.
President and Chief Executive Officer

Dear Dr. Carlo:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for epinephrine injection.

We also refer to the teleconference between representatives of your firm and the FDA on November 8, 2016. The purpose of the meeting was to discuss the June 3, 2016, complete response letter.

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

If you have any questions, call me at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Colette Jackson
Senior Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A
Meeting Category: Guidance

Meeting Date and Time: November 8, 2016, 2 PM to 3 PM EST
Meeting Location: WO22, Conference Room 1421

Application Number: NDA 207534
Product Name: epinephrine injection
Indication: Emergency treatment of allergic reactions (Type I) including anaphylaxis
Sponsor/Applicant Name: Adamis Pharmaceuticals Corporation

Meeting Chair: Badrul A. Chowdhury, M.D., Ph.D.
Meeting Recorder: Colette Jackson

FDA ATTENDEES

CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Pulmonary, Allergy, and Rheumatology Products

Badrul A. Chowdhury, M.D., Ph.D., Division Director
Lydia Gilbert-McClain, M.D., Deputy Division Director
Janet Maynard, M.D., Clinical Team Leader
Peter Starke, M.D., Clinical Reviewer
Colette Jackson, Senior Regulatory Health Project Manager

Office of Pharmaceutical Quality/Division of New Drug Products II

Venkateswara Pavuluri, Ph.D., CMC Reviewer
Craig Bertha, Ph.D., Quality Assessment Lead
Julia Pinto, Ph.D., Branch Chief

Office of Surveillance and Epidemiology

Lissa Owens, Pharm.D., Safety Evaluator, DMEPA
Lubna Merchant, Pharm.D., Acting Deputy Director, OMEPRM
Michael Sinks, Pharm.D., Regulatory Project Manager

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

Office of Combination Products

Patricia Love, M.D., Director

Office of Device Evaluation, General Hospital Devices Branch

Alan Stevens, M.S., Branch Chief

Kathleen Fitzgerald, Lead Device Reviewer

SPONSOR ATTENDEES

Adamis Pharmaceuticals

Dennis J. Carlo, Ph.D., President and Chief Executive Officer

Thomas Moll, Ph.D., Vice President Research

1.0 BACKGROUND

Adamis Pharmaceuticals sent in a Type A meeting request dated September 2, 2016, to discuss their June 3, 2016, complete response letter. The Division granted the meeting on November 9, 2016. Adamis Pharmaceuticals provided their briefing materials with the September 2, 2016, meeting request submission. The FDA sent Preliminary Comments to Adamis on November 4, 2016. On November 7, 2016, Adamis provided a clarification document to outline their points of discussion for the meeting. The email and clarification document are included in Section 6.0 Attachments and Handouts.

2. DISCUSSION

Introductory Comment

We note that in your submission dated December 4, 2015, to the Complete Response action on March 27, 2015, you redesigned your product (b) (4)

Specifically, the product proposed in the December 4, 2015, submission included (b) (4)

In your submission, you did not provide adequate data to support the safe and effective use of the redesigned epinephrine prefilled syringe for the emergency treatment of allergic reactions (Type I) including anaphylaxis. Despite limitations in the conduct of the human factors testing, the results demonstrated an unacceptably high failure rate in the performance of critical tasks that could result in serious harm because with these errors the users may not get the intended dose of epinephrine.

We note that you have now redesigned the prefilled device in response to our Complete Response letter of June 3, 2016, and wish to discuss the conduct of final human factors and other testing prior to submission of your complete response. We acknowledge that you have made changes to the device in an attempt to address the deficiencies previously noted, and plan to test this redesigned device in your human factors studies. The responses to the following questions are intended to assist you in your development program.

Question 1.1

Does FDA agree that the submitted protocol for human factors validation adequately represents the applicable user groups, use environments and use scenarios for the proposed Symjepi Prefilled Syringe for the emergency treatment of allergic reactions (Type I) including anaphylaxis?

FDA Response:

We have the following recommendations regarding the human factors validation protocol:

1. *It may be appropriate for the HF validation study to only test untrained users if it is not expected that training will be provided consistently for every intended user in actual use or you have reasonably established that training would not be generally expected to occur with your product.*
2. *You state that participants that are trained will have ‘at least a 24 hour decay period.’ If you proceed with a trained arm, ensure that all participants have the same decay period to maintain consistency.*
3. *Under Data Scoring, it appears that the resolved category may contain close calls and operational difficulties, ensure you capture all use errors, close calls, and operational difficulties as separate categories and submit a root cause analysis for each category. In addition, repeated attempts to complete a task and apparent confusion could indicate problems with the user interface; therefore, you should collect observational and subjective data on such repeated attempts/apparent confusion and debrief these occurrences with test participants to understand from their perspective the nature and potential root causes.*
4. *Under Data Scoring, you propose a category of “Not Assessed” and define this as “A task that was Not Assessed”. As examples, this may be due to insufficient time in the study or due to an incomplete prerequisite task”. However, if a participant requires additional time that exceeds the allotted timeframe to perform the injections, this should be noted in one of the above categories listed under #3 and adequate follow-up, including a root cause analysis, should be conducted to examine the cause of the additional time.*
5. *Under Data Collection and Coding you state “When appropriate, the Moderator may provide unrealistic assistance with a task (after scoring the task as a failure) to enable the assessment of subsequent steps” however, if a participant fails a task the moderator should not intervene. This is not representative of a real-world scenario. The error should be noted and the root cause should be determined.*

Discussion:

Adamis noted that they have encountered difficulties in obtaining adolescent subjects that are experienced users and asked the FDA if it is acceptable to include both adolescent subjects who have been trained to use the device, but not necessarily experienced in using it, and those who have experience using the device. The FDA stated that this approach is acceptable.

Question 1.2

Does FDA agree that successful conduct of the proposed human factors validation as per the protocol presented in Section 1.6.2.2 would provide adequate data to support the safe and

effective use of Symjepi for the emergency treatment of allergic reactions (Type I) including anaphylaxis?

FDA Response:

The adequacy of the results of the proposed human factors validation study will be a review issue.

Discussion:

No discussion was held for this response.

Question 1.3

Does FDA agree that providing adequate data to support the safe and effective use of the Symjepi product through the successful conduct and completion of the proposed human factors validation will fully address the deficiency identified in the Complete Response and will be sufficient to resubmit the application and start a new review cycle?

FDA Response:

Yes, we agree that providing adequate data to support the safe and effective use of the Symjepi product will be sufficient to resubmit the application and start a new review cycle.

Discussion:

No discussion was held for this response.

Question 2.1

Does FDA agree that either, a sample size of 500 with zero (0) failures, or a sample size of 1000 with two (2) failures will demonstrate an adequate confidence limit for the performance of the sharps prevention feature in the Symjepi product?

FDA Response:

Yes, we agree.

Discussion:

No discussion was held for this response.

Question 2.2

Does FDA agree that the results of the proposed additional sharps injury prevention failure testing can be amended to the application either at the time of resubmission, or as a separate amendment after the start of the new review cycle?

FDA Response:

Yes, we agree.

Discussion:

No discussion was held for this response.

Question 2.3

Does FDA agree that no additional biocompatibility testing will be required

(b) (4)

?

FDA Response:

We recommend that testing be conducted on the final finished device or components as manufacturing and processing can alter the material properties/biocompatibility. You may be able to leverage the testing performed from the components with identical materials; however, please provide a certification statement that the manufacturing and processing of the components are identical (see below) to the leveraged components. If there are any differences, please provide a rationale for how the manufacturing processes will not result in any changes to the material that would alter the biocompatibility (b) (4)

You have provided a list of materials used for User Contact parts (Table 3). Please include the material supplier, trade name, and CAS # in this table. The list of materials should include any additives as well as manufacturing and/or processing agents (e.g., plasticizers, fillers, color additives, cleaning agents, mold release agents).

Discussion:

Adamis referred to the materials table provided in their clarification document and asked if additional biocompatibility testing is needed. The FDA stated that no additional testing is needed if the materials are the same as previously provided and reviewed. The FDA suggested Adamis provide a side by side comparison of materials with details in their forthcoming NDA complete response submission.

POST-MEETING NOTE:

Please refer to the *Guidance for Industry: Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"*. It can be found at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM348890.pdf>. No additional testing would be required if as stated in the guidance under Attachment F:

Comparison to previous device: "The medical device in its final finished form is identical to [name] (previously marketed device) in formulation, processing, sterilization, and geometry and no other chemicals have been added (e.g., plasticizers, fillers, additives, cleaning agents, mold release agents)."

Question 2.4

Does FDA agree that the test protocols and test reports of the biocompatibility studies conducted can be amended to the application either at the time of resubmission, or as a separate amendment after the start of the new review cycle?

FDA Response:

Yes, we agree.

Discussion:

No discussion was held for this response.

Discussion held for New Adamis Question #3 in Clarification Document:

Adamis asked the Agency if it is possible to be granted an expedited review of their forthcoming NDA resubmission, which is expected to be submitted by December 31, 2016. The FDA stated that the review timeline for a resubmission is a 6-month review clock and the review will be conducted in a timely manner. However, the FDA is not able to commit to reviewing the submission sooner than the 6-month review time period.

The Agency asked Adamis to clarify the to-be-marketed packaging configuration for their product. Adamis stated they intend to market the product as a two-pack. The FDA asked Adamis if they would consider marketing both the single and two-pack configurations. The FDA noted that between 12% and 36% of patients may require a second dose while seeking emergency medical care. Thus, the majority of patients only need to replace the one used dose. Therefore, it would be convenient if both single- and two-packs were available. Adamis stated they are agreeable in marketing both configurations.

3.0 OTHER IMPORTANT MEETING INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 none of the criteria apply at this time to your application, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

505(b)(2) REGULATORY PATHWAY

The Division recommends that 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 draft guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999), 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 that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, 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(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each 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 or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA’s finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA’s consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA’s finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to 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 published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication A</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section B</i>
<i>4.</i>	

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 a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to 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 Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion]

5.0 ACTION ITEMS

There were no action items that were identify during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

November 7, 2016, email from Adamis and their points of clarification document.

Jackson, Colette

From: Dennis Carlo <dcarlo@adamispharma.com>
Sent: Monday, November 07, 2016 1:41 PM
To: Jackson, Colette
Subject: Reply to: Adamis meeting 11/8/16 - FDA Preliminary Meeting Comments: PLEASE CONFIRM RECEIPT
Attachments: FDA ltr Type A Meeting 11.8.16.pdf

Colette,

Thank you very much for sending the FDA preliminary meeting responses.

In view of the responses provided we feel that a face to face meeting may no longer be required. However, we do have a couple of points for which we would like to seek further clarification and we would propose to proceed with a teleconference call at the originally scheduled time, i.e. tomorrow, November 8th, at 2PM Eastern Time.

The dial-in information for the call is:

Dial-in Number: (701) 801-1220

Meeting ID (b) (6)

The items for which we are looking for further clarification are outlined in the attached letter.

We would very much appreciate it if you could confirm the conference call (November 8, 2PM Eastern Time).

Best regards,

Dennis J. Carlo, Ph.D.

President & CEO

ADAMIS PHARMACEUTICALS CORPORATION

11682 El Camino Real, Ste 300, San Diego, CA 92130

Direct Office: 858.412-7943 | Main Office: 858.997.2400

dcarlo@adamispharma.com



adamispharmaceuticals.com

Please consider the environment before printing this email.

CONFIDENTIALITY NOTICE

The information contained in this email may be confidential and/or legally privileged. It has been sent for the sole use of the intended recipient(s). If the reader of this message is not an intended recipient, you are hereby notified that any unauthorized review, use, disclosure, dissemination, distribution, or copying of this communication, or any of its contents, is strictly prohibited. If you have received this communication in error, please reply to the sender and destroy all copies of the message.

From: Jackson, Colette [mailto:Colette.Jackson@fda.hhs.gov]
Sent: Friday, November 4, 2016 10:26 AM
To: Dennis Carlo <dcarlo@adamispharma.com>
Subject: RE: Adamis meeting 11/8/16 - FDA Preliminary Meeting Comments: PLEASE CONFIRM RECEIPT
Importance: High

Dear Dr. Carlo,

Attached are our FDA preliminary meeting responses for NDA 207534 in preparation for our meeting with Adamis on Tuesday, November 8th. Please confirm receipt via reply to this email.

As soon as your review team has reviewed our comments, please let me know how you would like to proceed (i.e., cancel the meeting, change the meeting to a tcon, or continue with the face to face meeting). If your team decides to have the meeting (tcon or face to face), please outline those items requiring discussion at the meeting in an email to me by COB Monday, November 7th. Please note we will not be able to entertain any new data or information at the meeting and the discussion will focus on clarification of our responses provided.

Let me know if you have any questions.

Kind Regards,

Colette Jackson

*Senior Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue, Bld 22 Room 3322
Silver Spring, MD 20993-0002
Phone: 301-796-1230
FAX: 301-796-9718/9728
E-mail: Colette.Jackson@fda.hhs.gov*

From: Dennis Carlo [mailto:dcarlo@adamispharma.com]
Sent: Wednesday, November 02, 2016 1:00 PM
To: Jackson, Colette
Subject: Adamis meeting 11/8/16 - Please read and confirm receipt

Colette,

I sent you an email on Monday with our final list of attendees for next weeks' meeting, as well as a request to confirm that we will have access to the equipment needed to show a brief PowerPoint presentation (we will have a laptop and USB stick, but need to ensure that a projection screen or projector will be available). I have not heard back from you so am sending this follow-up email. Please confirm that you received the email and will have the projection screen/projector available for our use.

I also wanted to specify with regards to the participant list I sent that (b) (4) is a Regulatory Consultant for Adamis and that (b) (4) is a Statistical Consultant for Adamis.

Best regards,

Dennis J. Carlo, Ph.D.

President & CEO

ADAMIS PHARMACEUTICALS CORPORATION

11682 El Camino Real, Ste 300, San Diego, CA 92130

Direct Office: 858.412-7943 | Main Office: 858.997.2400

dcarlo@adamispharma.com



[adamis pharmaceuticals.com](http://adamispharmaceuticals.com)

Please consider the environment before printing this email.

CONFIDENTIALITY NOTICE

The information contained in this email may be confidential and/or legally privileged. It has been sent for the sole use of the intended recipient(s). If the reader of this message is not an intended recipient, you are hereby notified that any unauthorized review, use, disclosure, dissemination, distribution, or copying of this communication, or any of its contents, is strictly prohibited. If you have received this communication in error, please reply to the sender and destroy all copies of the message.



Dennis J. Carlo, Ph.D.
President and CEO

Phone: 858-412-7943
Fax: 858-356-6472

Colette Jackson
Senior Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

November 7, 2016

Re: NDA 207534 – Type A Meeting on November 8, 2016; Acknowledgement of Receipt of Preliminary Comments and Request to Hold Meeting as Teleconference Call

Dear Ms Jackson,

Thank you very much for sending the FDA preliminary meeting responses.

In view of the responses provided, and the busy year end schedule your colleagues have, we feel that a face to face meeting may no longer be required. However, we do have a couple of points for which we would like to seek further clarification and we would propose to proceed with a teleconference call at the originally scheduled time, i.e. tomorrow, November 8th, at 2PM Eastern Time.

The dial-in information for the call is:

Dial-in Number: (b) (6)

Meeting ID: (b) (6)

The items for which we are looking for further clarification are:

Question 1.1 Human Factors Protocol

We have encountered difficulties in identifying autoinjector experienced adolescent patients, where “experienced” is defined as adolescent patients that have previously self-administered epinephrine by use of an autoinjector. Would it be acceptable to expand the definition of



Dennis J. Carlo, Ph.D.
President and CEO
Phone: 858-412-7943
Fax: 858-356-6472

“experienced” to adolescent patients that have previously been prescribed an epinephrine autoinjector or been trained on the use of an epinephrine autoinjector?

Question 2.3 Biocompatibility

An expanded Table with additional information on the materials used is included below. Also, Adamis would be able to certify that:

- [REDACTED] (b) (4)
- [REDACTED] (b) (4)

Would inclusion of this additional information be sufficient to document biocompatibility of the finished device and obviate the need for additional biocompatibility testing?

Component	Generic Material	Base Resin	Colorant	Colorant Let Down Ratio
Top Housing	[REDACTED] (b) (4)			
Bottom Housing				
Needle Guard				
Actuator				
(b) (4)				
Cap*				
Case				

(b) (4)



Dennis J. Carlo, Ph.D.
President and CEO
Phone: 858-412-7943
Fax: 858-356-6472

We believe that our Human Factors study and a large questionnaire of EpiPen users strongly suggest that there are "Public Health Benefits" that our pre-filled syringe provides. They are as follows: (1) small size promotes portability and increased access; (2) simplicity of use increases utilization; and (3) low cost alternative allows greater access to a life saving drug.

Question 3 (New)

Based on the limited amount of additional information that is required, and the aforementioned public health benefits, we would like to request that you consider an expedited review of the resubmission.

We would very much appreciate it if you could confirm the conference call (November 8, 2PM Eastern Time).

Please contact me at (858) 412-7943 with any questions.

Sincerely,

A handwritten signature in cursive script that reads "Dennis J. Carlo".

Dennis J. Carlo, Ph.D.
President and Chief Executive Officer
Adamis Pharmaceuticals Corporation
11682 El Camino Real, Suite 300
San Diego, CA 92130
Tel: +1(858) 412 7943
Fax: +1(858) 461 0842

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

/s/

COLETTE C JACKSON
02/09/2017



NDA 207534

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Adamis Pharmaceuticals Corporation
11682 El Camino Real, Suite 300
San Diego, CA 92130

ATTENTION: Dennis J. Carlo, Ph.D.
President and Chief Executive Officer

Dear Dr. Carlo:

Please refer to your New Drug Application (NDA) dated and received December 15, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Epinephrine Injection, 0.3 mg/0.3 mL.

We also refer to your correspondence, dated and received December 15, 2016, requesting review of your proposed proprietary name, Symjepi.

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

If any of the proposed product characteristics as stated in your December 15, 2016 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

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

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

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Michael Sinks, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-2684. For any other information regarding this application, contact Colette Jackson, Regulatory Project Manager, in the Office of New Drugs at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

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

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

/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
02/08/2017



NDA 207534

**PROPRIETARY NAME
ACKNOWLEDGEMENT**

Adamis Pharmaceuticals Corporation
11682 El Camino Real, Suite 300
San Diego, CA 92130

ATTENTION: Dennis J. Carlo, Ph.D.
President and Chief Executive Officer

Dear Dr. Carlo:

Please refer to your New Drug Application (NDA) dated and received December 15, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Epinephrine Injection, 0.3 mg/0.3 mL.

We acknowledge receipt of your correspondence, dated and received December 15, 2016, requesting a review of your proposed proprietary name, Symjepi.

The user fee goal date is March 15, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Michael Sinks, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-2684. For any other information regarding this application, contact Colette Jackson, Regulatory Project Manager, in the Office of New Drugs at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Neil Vora, PharmD, MBA
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

NEIL VORA
02/06/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207534

**ACKNOWLEDGE –
CLASS 2 RESUBMISSION**

Adamis Pharmaceuticals Corporation
11682 El Camino Real, Suite 300
San Diego, CA 92130

Attention: Dennis J. Carlo, Ph.D.
President and Chief Executive Officer

Dear Dr. Carlo:

We acknowledge receipt on December 15, 2016, of your December 15, 2016, resubmission to your supplemental new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for epinephrine injection.

We consider this a complete, class 2 response to our June 3, 2016, action letter. Therefore, the user fee goal date is June 15, 2017.

If you have any questions, call me at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Colette Jackson
Senior Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

COLETTE C JACKSON
12/23/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 207534

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Adamis Pharmaceuticals Corporation
11682 El Camino Real
Suite 300
San Diego, CA 92130

ATTENTION: Dennis J. Carlo, Ph.D.
President and CEO

Dear Dr. Carlo:

Please refer to your New Drug Application (NDA) dated and received December 4, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Epinephrine Injection, 0.3 mg/0.3 mL.

We also refer to your correspondence, dated and received February 11, 2016, requesting review of your proposed proprietary name, Symjepi.

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

If any of the proposed product characteristics as stated in your February 11, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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 Michael Sinks, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 240-402-2684. For any other information regarding this application, contact Colette Jackson, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

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

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

/s/

TODD D BRIDGES
05/06/2016



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

DATE: April 25, 2016

To: Dennis J. Carlo	From: Colette Jackson
Company: Adamis Pharmaceuticals Corp	Division of Pulmonary, Allergy, and Rheumatology Products
Email Address: dcarlo@adamispharma.com	Fax number: 301-796-9718
Phone number: 858-412-7943	Phone number: 301-796-1230
Subject: NDA 207534 Epinephrine Injection- FDA Information Request	

Total no. of pages including cover: 5

Comments:

Document to be mailed:	YES	xNO
-------------------------------	------------	------------

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 207534
Adamis Pharmaceuticals Corporation
Epinephrine Injection USP (b) (4)

We refer to your December 4, 2015, NDA resubmission for Epinephrine Injection. We have the following comments and requests for information.

1. **Needle Design Verification /Validation**

The labeling and training instruct users to perform epinephrine injection through clothing. Review of the submission does not identify any design requirements for the injector, needle, or assembled combination product to specify adequately reliable injection through clothing. In addition to having explicit requirements for injection through clothing, the design requirements documentation should specify adequately valid requirements for the needle to assure that the needle will not bend, break or separate from the syringe during injection through clothing. Consideration of human factors should be considered during development and validation of the needle requirements. Additionally, FDA was unable to locate any performance data to verify and validate that the combination product will reliably inject epinephrine to the target injection site when injected through clothing. Clothing attributes might include material type, density, thickness, etc. Provide evidence that the combination product will reliably inject epinephrine to the target injection when the injection occurs through clothing. The evidence should include design requirements and performance data with adequately challenging conditions (e.g., sample size, clothing types, injection angles, transversely applied stress (transverse to injection angle), etc.).

2. **Reliability**

The intended use of your product involves the delivery of medication to treat a potentially life threatening condition within use environments that may offer limited opportunity for alternative treatments. As such, the Agency believes that it is essential for your product to perform reliably. The NDA does not include adequate documentation to verify that the combination product will reliably inject epinephrine throughout the expiry period. Product reliability should be supported by explicit reliability specifications, risk analysis, and performance data. Therefore, we are requesting that you establish reliability requirements for the combination product and complete testing which verifies combination product reliability.

Provide the following:

- a. Establish reliability requirements for your combination product. We recommend that reliability be directly specified as $R(t) = x\%$, where t = time and $x\%$ = probability of meeting essential performance requirements. These requirements should be objective and relate to the ability of a population of devices to meet essential performance requirements after pre-conditioning to elements outlined within c, below. The reliability requirements should be verified with a high degree of statistical confidence.
- b. Provide rationale and justification supporting the clinical acceptability of the established reliability requirements.

- c. Provide protocols and data to verify the reliability requirements specified have been met.
- d. Final assembled combination products that are assessed within the reliability test should be preconditioned to worst-case reasonably foreseeable conditions. The Agency has conceived the following recommended preconditioning activities, however, you should provide rationale supporting the final precondition elements chosen, and the order in which the products are conditioned. Your assessment of the preconditioning parameters should be based on your own failure analyses (e.g., fault tree analysis) in order to assure that the scope of preconditions and their boundary values are adequately correct and complete. All preconditioning and test methodologies should be validated per your risk analysis and reliability requirements.
 - i. Shipping
 - ii. Aging
 - iii. Storage orientation and conditions
 - iv. Vibration
 - v. Shock (e.g., resistance to random impacts, such as being dropped)
- e. Devices assessed within the reliability analysis should be activated under worst-case reasonably foreseeable conditions. The Agency has conceived the following recommended circumstances of activation; however, you should provide rationale supporting the final circumstances of activation chosen.
 - i. Activation orientation
 - ii. Environmental temperature
 - iii. Injection site conditions (clothing type, skin type, etc.)

3. **Sharps Injury Prevention**

The redesigned fully assembled EPINEPHRINE INJECTION prefilled syringe combination product has a needle guard to prevent accidental needle sticks. You have provided testing for the force required to deploy the sharps injury prevention feature but you have not completed testing that demonstrates the sharps injury prevention feature is reliable and the failure rate. Please complete testing on the sharps injury prevention feature and reference the following documents.

- Guidance for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features.

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071663.htm>

- ISO 23908:2011: Sharps injury protection -- Requirements and test methods – Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling.

4. **Biocompatibility**

The redesigned combination product contains

(b) (4)

No biocompatibility test reports were located on the new redesigned combination product device parts. The Agency recommends that you perform biocompatibility testing on the final finished device. Please provide the following biocompatibility test protocols and test reports based on ISO 10993-1 on all patient-contacting components on the final finished device.

- a) *In vitro* cytotoxicity testing based on ISO 10993 Biological evaluation of medical devices, Part 5 Test for *in vitro* cytotoxicity;
 - b) Irritation testing based on ISO 10993 Biological evaluation of medical devices, Part 10 Tests for irritation and skin sensitization;
 - c) Delayed hypersensitivity testing based on ISO 10993 Biological evaluation of medical devices, Part 10 Tests for irritation and skin sensitization.
5. Please provide a detailed side-by-side comparison of the original combination product design and the new redesign combination product in NDA 207534.
 6. In the accelerated aging studies you state the week 4 samples (simulated 12 month real time aging), exhibited partial separation of the top housing and bottom housing on 7 of the 20 samples analyzed. You state that assemblies remained intact and all samples passed functional testing. Please determine the root cause of the device separation and proposed corrective actions. Also, please complete dose accuracy testing after accelerated aging studies are completed.
 7. Please explain the functionality of the spring in the device components.

In order to facilitate our review, we ask you provide a response by COB May 3, 2016, by email at Colette.Jackson@FDA.HHS.GOV or facsimile to 301-796-9728, followed by an official submission to the application. If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Drafted: Colette Jackson/April 25, 2016

Initialed: Sandy Barnes/ April 25, 2016
Julia Pinto/ April 20, 2016
Craig Bertha/ April 25, 2016

Finalized: CCJ/ April 25, 2016

Filename: 207534 CDRH ODE fax April 2016.doc

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

/s/

COLETTE C JACKSON
04/25/2016



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II**

ELECTRONIC CORRESPONDENCE

DATE: April 21, 2016

To: Dennis J. Carlo	From: Colette Jackson
Company: Adamis Pharmaceuticals Corp	Division of Pulmonary, Allergy, and Rheumatology Products
Email Address: dcarlo@adamispharma.com	Fax number: 301-796-9718
Phone number: 858-412-7943	Phone number: 301-796-1230
Subject: NDA 207534 Epinephrine Injection- FDA Information Request	

Total no. of pages including cover: 3

Comments:

Document to be mailed:	YES	xNO
-------------------------------	------------	------------

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 207534
Adamis Pharmaceuticals Corporation
Epinephrine Injection USP (b) (4)

We refer to your December 4, 2015, NDA resubmission for Epinephrine Injection. We request the following information to demonstrate your compliance with 21 CFR 820.30 (Design Controls), 21 CFR 820.50 (Purchasing Controls), and 21 CFR 820.100 (CAPA).

1. Your firm provided information pertaining to design planning, design input, design output, design verification and design validation. Provide information pertaining to design changes for the proposed finished combination product.
2. A description of your firm's supplier evaluation process and a description of your firm's purchasing controls, including information on how your firm will balance purchasing assessment and receiving acceptance to ensure products and services are acceptable for their intended use. Include a description of supplier evaluation process and a description of purchasing controls at the combination product manufacturer (b) (4)
3. A description of your firm's corrective and preventive action (CAPA) system, including how your CAPA system communicates between the different sites that are involved in the manufacturing of the combination product. Include a description of supplier evaluation process and a description of purchasing controls at the combination product manufacturer (b) (4)

In order to facilitate our review, we ask you provide a response by COB April 26, 2016, by email at Colette.Jackson@FDA.HHS.GOV or facsimile to 301-796-9728. If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Drafted: Colette Jackson/April 19, 2016

Initialed: Sandy Barnes/ April 19, 2016

Julia Pinto/ April 18, 2016

Craig Bertha/ April, 2016

Finalized: CCJ/ April 21, 2016

Filename: 207534 CDRH OC fax April 2016.doc

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

/s/

COLETTE C JACKSON
04/21/2016



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II**

ELECTRONIC CORRESPONDENCE

DATE: March 24, 2016

To: Dennis J. Carlo	From: Colette Jackson
Company: Adamis Pharmaceuticals Corp	Division of Pulmonary, Allergy, and Rheumatology Products
Email Address: dcarlo@adamispharma.com	Fax number: 301-796-9718
Phone number: 858-412-7943	Phone number: 301-796-1230
Subject: NDA 207534 Epinephrine Injection- FDA Information Request	

Total no. of pages including cover: 3

Comments:

Document to be mailed:	YES	xNO
-------------------------------	------------	------------

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 207534
Adamis Pharmaceuticals Corporation
Epinephrine Injection USP (b) (4)

We refer to your December 4, 2015, NDA resubmission for Epinephrine Injection. We have the following comment and request for information.

We observed that the stability data submitted for primary stability lots at resubmission are not completely the same as what were submitted in the original application. Provide an explanation of the differences in the two sets of stability data, especially with respect to the levels of individual and total unknown impurities as noted here. In original submission reported values for individual unknown impurities with RRT (b) (4) (at 12 months) and RRT (b) (4) (at 18 months) were (b) (4) % for lot EP0003, but the reported values for the two unknown impurities (in same batch) at the same time points in resubmission are (b) (4) (b) (4) %.

In order to facilitate our review, we ask you provide a response by COB March 31, 2016. If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Drafted: Colette Jackson/March 24, 2016

Initialed: Sandy Barnes/ March 24, 2016
Venkat Pavuluri/ March 22, 2016
Craig Bertha/ March 22, 2016
Julia Pinto/ March 22, 2016

Finalized: CCJ/ March 24, 2016

Filename: 207534 CMC fax March 2016.doc

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

/s/

COLETTE C JACKSON
03/24/2016



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II**

ELECTRONIC CORRESPONDENCE

DATE: March 16, 2016

To: Dennis J. Carlo	From: Colette Jackson
Company: Adamis Pharmaceuticals Corp	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 858-461-0842	Fax number: 301-796-9718
Phone number: 858-412-7943	Phone number: 301-796-1230
Subject: NDA 207534 Epinephrine Injection- FDA Information Request	

Total no. of pages including cover: 3

Comments:

Document to be mailed:	YES	xNO
-------------------------------	------------	------------

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 207534
Adamis Pharmaceuticals Corporation
Epinephrine Injection USP (b) (4)

We refer to your March 15, 2016, submission for Epinephrine Injection. We have the following comments and requests for information.

We note that you only submitted the summary of your human factors formative and validation studies. We request that you submit the following as soon as possible for our review:

1. Formative studies and results, including a discussion of key findings and any changes made to your product or labeling, including how the findings were used to update the user interface and risk analysis.
2. Comprehensive use-related risk analysis for your product.
3. Human Factors (HF) validation protocol and results, to include the following elements:
 - a. User task selection, categorization (e.g., critical) and prioritization
 - b. HF validation test objective(s)
 - c. Type of testing (simulated or actual use)
 - d. Test environment and conditions of use
 - e. Training provided to participants and rationale for how it corresponds to real-world training
 - f. Distinct user groups broken out by number and type of test participants and rationale for how they represent the intended user population
 - g. User tasks and use scenarios selected
 - h. Description of data collected and methods for documenting observations and interview responses
 - i. Definition of performance success and performance failure
 - j. Methods for root cause analysis of all use errors, difficulties, close calls
 - k. Study results (use errors, difficulties, close calls) and root cause analysis
 - l. Moderator transcript
4. Intend-to-market labels and labeling (including an editable word version of the Instructions for Use that was tested in the HF validation study).
5. Any additional training materials used in the HF validation study and/or will be used for training (e.g., training video, mobile app).

In order to facilitate our review, we ask you provide a response by COB March 23, 2016. If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Finalized: CCJ/ March 16, 2016

Filename: 207534 DMEPA fax March 2016.doc

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

/s/

COLETTE C JACKSON
03/16/2016



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II**

FACSIMILE TRANSMITTAL SHEET

DATE: March 3, 2016

To: Dennis J. Carlo	From: Colette Jackson
Company: Adamis Pharmaceuticals Corp	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 858-461-0842	Fax number: 301-796-9718
Phone number: 858-412-7943	Phone number: 301-796-1230
Subject: NDA 207534 Epinephrine Injection- FDA Information Request	

Total no. of pages including cover: 3

Comments:

Document to be mailed:	YES	xNO
-------------------------------	------------	------------

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 207534
Adamis Pharmaceuticals Corporation
Epinephrine Injection USP (b) (4)

We refer to your December 4, 2015, NDA resubmission for Epinephrine Injection. We have the following comments.

1. (b) (4)
(b) (4)
We are concerned that (b) (4)
(b) (4) patients and caregivers may think that the proposed product is an autoinjector. This could lead to difficulty administering the product during anaphylaxis because the injection steps for the proposed product are different than the injection steps for an autoinjector and there is a risk of negative transfer if this is used by previous epinephrine autoinjector users. We have the following requests for information:
 - a. Clarify if the proposed design been marketed for any other products. If so, please provide a summary of all complaints and errors seen with these other products.
 - b. In the development of this new product, please clarify if Human Factors studies were performed to support the use of this product in an emergency situation. If so, provide a summary of preliminary analyses and evaluations, including formative studies; include in your summary a discussion of key findings and any changes made to your product or labeling, including how the findings were used to update the user interface and risk analysis. Provide your human factors validation protocol, and the results of those studies.
2. We note that, in addition to the epinephrine injection solution, the prefilled syringe contains a bubble. Please confirm (b) (4)
(b) (4)
3. In your submission under 3.2.P.2.4.2.3.3 *Delivery Rate and Orientation Testing* it was indicated that “when a bubble is present in the syringe, in order to assure dose volume accuracy the device must be oriented by end users in the intended use orientation with the needle pointing down.” Provide data that indicate the magnitude (mean and range) of the decrease in dose if patients do not use the device with the needle pointing down. If the dose delivered is not within the target

range regardless of the needle position (b) (4)

4. In the certificate of analysis provided for an additional batch of drug substance tested (Batch 7691881) as per the revised specification, the test results for (b) (4) content were stated as (b) (4) % (as per Ph Eur) and (b) (4) % (as per USP). Provide the actual test results obtained (b) (4) for the drug substance batch # 7691881, instead of the general statements, i.e. (b) (4) % (as per Ph Eur) and (b) (4) % (as per USP).

In order to facilitate our review, we ask you provide a response by COB March 15, 2016. If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Drafted: Colette Jackson/March 1, 2016

Initialed: Sandy Barnes/ March 1, 2016

Peter Starke/ March 1, 2016

Janet Maynard/ March 1, 2016

Craig Bertha/ March 1, 2016

Julia Pinto/ March 1, and 2, 2016

Finalized: CCJ/ March 3, 2016

Filename: 207534 MO and CMC fax March 2016.doc

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

/s/

COLETTE C JACKSON
03/03/2016

Rashid, Nichelle E

From: Rashid, Nichelle E
Sent: Monday, February 08, 2016 3:59 PM
To: Thomas Moll
Cc: Jackson, Colette; Dennis Carlo; Rashid, Nichelle E
Subject: RE: NDA 207534 December 4, 2015, Resubmission

Follow Up Flag: Follow up
Flag Status: Flagged

Categories: Completion of Tasks

Good Afternoon Dr. Moll,

As noted previously in Ms. Jackson's email below and in our CR letter, the trade name is conditional pending approval and must be resubmitted with your response to the CR letter.

We noted that your Request for Proprietary Name Review for Symjepi has not been submitted.

Please submit the proprietary name request this week.

If you have any questions, please do not hesitate to contact me.

Thanks,

Nichelle E. Rashid
Senior Safety Regulatory Health Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Tel: (301) 796-3904
Fax: (301) 796-9725
nichelle.rashid@fda.hhs.gov

From: Thomas Moll [<mailto:tmoll@adamispharma.com>]
Sent: Monday, January 11, 2016 7:38 PM
To: Jackson, Colette; Dennis Carlo
Cc: Rashid, Nichelle E; Thomas Moll
Subject: RE: NDA 207534 December 4, 2015, Resubmission

Dear Ms Jackson,

Thank you very much for your e-mail.

In the cover letter of the December 4, 2015 NDA 207534 resubmission (sequence # 0011) Adamis acknowledged that FDA had found the proposed proprietary name, Symjepi, acceptable, and requested to proceed with the use of the same name for the product (see Cover Letter, page 5, section 1.3).

As Adamis wishes to proceed with the use of the same proprietary name and there have been no changes to the Proprietary Name Request submitted earlier, the Company has therefore, in the cover letter, referenced the original Proprietary Name Request as part for the current submission.

A copy of the cover letter containing the request is attached. Dr. Carlo will try to give you a call tomorrow morning to follow up.

Thank you very much again and best regards,

Thomas Moll

Thomas Moll, PhD
Vice President Research



11682 El Camino Real, Suite 300
San Diego, CA 92130
USA

Tel: +1 (858) 412 7946

Cell: (b) (6)

tmoll@adamispharma.com

From: Jackson, Colette [<mailto:Colette.Jackson@fda.hhs.gov>]
Sent: Monday, January 11, 2016 3:13 PM
To: Dennis Carlo <dcarlo@adamispharma.com>; Thomas Moll <tmoll@adamispharma.com>
Cc: Rashid, Nichelle E <Nichelle.Rashid@fda.hhs.gov>
Subject: NDA 207534 December 4, 2015, Resubmission
Importance: High

Dear Dr. Carlo,

We have received the December 4, 2015, resubmission for NDA 207534 in response to our March 27, 2015, complete response (CR) letter. Please note that we do not see a new Proprietary Name Request submitted with this resubmission. As outlined in our CR letter, the trade name is conditional pending approval and must be resubmitted with your response to the CR letter.

Please submit the proprietary name request ASAP.

Thank you,

Colette Jackson
Senior Regulatory Health Project Manager

*Division of Pulmonary, Allergy, and Rheumatology Products
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue, Bld 22 Room 3322
Silver Spring, MD 20993-0002
Phone: 301-796-1230
FAX: 301-796-9718/9728
E-mail: Colette.Jackson@fda.hhs.gov*

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

/s/

NICHELLE E RASHID
02/22/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207534

**ACKNOWLEDGE –
CLASS 2 RESUBMISSION**

Adamis Pharmaceuticals Corporation
11682 El Camino Real, Suite 300
San Diego, CA 92130

Attention: Dennis J. Carlo, Ph.D.
President and Chief Executive Officer

Dear Dr. Carlo:

We acknowledge receipt on December 4, 2015, of your December 4, 2015, resubmission to your supplemental new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for epinephrine injection.

We consider this a complete, class 2 response to our March 27, 2015, action letter. Therefore, the user fee goal date is June 4, 2016.

If you have any questions, call me at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Colette Jackson
Senior Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

COLETTE C JACKSON
01/13/2016



NDA 207534

MEETING MINUTES

Adamis Pharmaceuticals Corporation
11682 El Camino Real, Suite 100
San Diego, CA 92130

Attention: Dennis J. Carlo, Ph.D.
President and Chief Executive Officer

Dear Dr. Carlo:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for epinephrine injection.

We also refer to your June 19, 2015, correspondence, received June 19, 2015, requesting a meeting to discuss Letter.

We also refer to the meeting between representatives of your firm and the FDA on August 5, 2015. The purpose of the meeting was to discuss your March 27, 2015, Complete Response letter.

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, call me at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Colette Jackson
Senior Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A
Meeting Category: Guidance

Meeting Date and Time: August 5, 2015, at 3PM EST
Meeting Location: via teleconference

Application Number: NDA 207534
Product Name: epinephrine injection
Indication: Emergency treatment of allergic reactions (Type I) including anaphylaxis
Sponsor/Applicant Name: Adamis Pharmaceuticals Corporation

FDA ATTENDEES:

CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Pulmonary, Allergy, and Rheumatology Products

Badrul A. Chowdhury, M.D., Ph.D., Division Director
Lydia Gilbert-McClain, M.D., Deputy Division Director
Janet Maynard, M.D., Clinical Team Leader
Peter Starke, M.D., Clinical Reviewer
Colette Jackson, Senior Regulatory Health Project Manager

Office of Pharmaceutical Quality/Division of New Drug Products II

Craig Bertha, Ph.D., Quality Assessment Lead
Julia Pinto, Ph.D., Branch Chief

SPONSOR ATTENDEES

Adamis Pharmaceuticals

Dennis J. Carlo, Ph.D., President and Chief Executive Officer
Thomas Moll, Ph.D., Vice President Research
Karen Daniels, Vice President, Operations

(b) (4)

(b) (4) Regulatory Consultant

1.0 BACKGROUND

Adamis Pharmaceuticals sent in a Type A meeting request dated June 19, 2015, to discuss their March 27, 2015, complete response letter. The Division granted the meeting on July 3, 2015. Adamis Pharmaceuticals provided their briefing materials with the June 19, 2015, meeting request submission.

2.0 DISCUSSION

Question 1.1

Does the Division agree that providing this information will be sufficient for resubmission of the application and fully address all the deficiencies listed in Product Quality, Section 1 of the CRL?

FDA Response:

The summary of the information that will be provided in response appears to be reasonable. The determination of whether or not the information and data fully address the CR letter deficiencies will be determined following a review of the resubmission.

Question 1.2

Does the Division agree that,

(b) (4)

1. It will be appropriate to use a single batch of epinephrine solution filled and stoppered syringes to conduct the

(b) (4)

performance testing and validation?

2. No additional validation batch data or validation reports for drug product formulation or syringe filling and stoppering are required for resubmission of the application?

3. No additional drug product stability data are required for resubmission of the application?

FDA Response:

Yes, we agree.

Question 2.1 – 2.4

Can the Agency confirm that the request made in Product Quality, Section 2 of the CRL refers to "container content", i.e. the "extractable volume" of the syringe as used in the Certificate of Analysis issued by the drug product manufacturer, a term which the manufacturer uses interchangeably with the term "container content" as used in USP <1>?

If the answer to question 2.1 above is no, and the request made in Product Quality, Section 2 of the CRL does not refer to "container content", can the Division confirm whether the request refers to the "deliverable volume" of the product?

Does the Agency agree that the determination of "container content" of the Epinephrine Injection prefilled syringe does not require validation or verification, if the compendia analytical procedure described in USP <1> is used?

Does the Agency agree that the determination of "deliverable volume" of the Epinephrine Injection prefilled syringe does not require validation or verification, if the compendia analytical procedure for "container content" in prefilled syringes, as described in USP <1> is used?

FDA Response:

Your meeting package provides some more clarification about how the container content and the deliverable volume are determined. It appears that the manufacturer uses (b) (4) to evaluate these parameters. Based on this limited description, we have several concerns that you should to address when preparing your resubmission:

1. The application should contain regulatory methods that the Agency laboratories can follow for testing of the drug product to its specification, including tests for the parameters of container content and deliverable volume. From your description of these tests performed (b) (4)
2. It is reasonable (b) (4) to determine the container content (b) (4) but this should be considered to be an alternate method. There should be a regulatory method that our laboratory can follow to measure this parameter on the final drug product (as provided to patients), and this method should be demonstrated to provide equivalent results to the (b) (4) method. This regulatory method should be described as part of the application.
3. Because of the importance of the determination of the deliverable volume (which in part, determines the dose the patient receives), this determination should be done for the final drug product as it will be received by patients, and not with some type of (b) (4)

It is because of this lack of clarity about these volume tests that we had asked that you provide written and detailed methods (b) (4) Your resubmission should be clear and describe how these tests are carried out and also address the above concerns regarding the regulatory methods.

Discussion:

Adamis Pharmaceuticals (Adamis) asked the FDA for clarification of the testing required for the parameters of container content and deliverable volume and at which time points during product

assembly should the testing be conducted. Adamis proposes to determine the deliverable volume on the final drug product and provide the acceptance criteria in the resubmission. For container content, Adamis proposes to use regulatory methods on the final drug product as provided to patients. Adamis will develop these methods and include this information in the resubmission. The FDA stated that their proposal is acceptable and is consistent with our points 2 and 3 in the response above.

Adamis asked the FDA about the review timeframe for the resubmission. The FDA explained that the resubmission would be classified as a Class 2 resubmission with a 6 month review clock as there will be a need for a facilities inspection in light of the proposed changes to the final drug product.

Question 3.1 & 3.2

Does the Division agree that matching the drug substance supplier specification by testing for (b) (4) using the Ph.Eur. compendia method, and verification of the method in accordance with USP <1226>, will appropriately address the issue raised by the Agency?

Does the Division agree that testing and reporting residual solvent in the drug substance in accordance with USP <467> and amending the drug substance specification to include the residual solvent (b) (4) (acceptance criterion (b) (4) ppm) will appropriately address the issue raised by the Agency?

FDA Response:

Yes, we agree. However, as per 21 CFR 211.84(d)(2), you have the responsibility of establishing the reliability of the supplier's test results through appropriate validation at appropriate intervals.

Additional Comments

We expect that the depth of needle penetration into the body will not change with the redesigned version of your drug product. Provide specific comparison of the maximum exposed needle length before and after the redesign.

3.0 OTHER IMPORTANT MEETING INFORMATION

PREA REQUIREMENTS

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant

endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items identified at the meeting.

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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

/s/

COLETTE C JACKSON
09/04/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 207534

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Adamis Pharmaceuticals Corporation
11682 El Camino Real
Suite 300
San Diego, CA 92130

ATTENTION: Dennis J. Carlo, Ph.D.
President and Chief Executive Officer

Dear Dr. Carlo:

Please refer to your New Drug Application (NDA) dated and received May 28, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Epinephrine Injection, 0.3 mg/0.3 mL.

We also refer to your correspondence, dated and received December 12, 2014, requesting review of your proposed proprietary name, Symjepi. We have completed our review of the proposed proprietary name, Symjepi and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your December 12, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application, contact Colette Jackson, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology

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

/s/

TODD D BRIDGES
03/02/2015



NDA 207534

DEFICIENCIES PRECLUDE DISCUSSION

Adamis Pharmaceuticals Corporation
11682 El Camino Real, Suite 100
San Diego, CA 92130

Attention: Dennis J. Carlo, Ph.D.
President and Chief Executive Officer

Dear Dr. Carlo:

Please refer to your New Drug Application (NDA) dated May 23, 2014, received May 28, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for epinephrine injection.

We also refer to our August 6, 2014, letter in which we notified you of our target date of February 28, 2015, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals And Procedures – Fiscal Years 2013 Through 2017."

As part of our ongoing review of your application, we have identified deficiencies that preclude discussion of labeling and postmarketing requirements/commitments at this time.

This notification does not reflect a final decision on the information under review.

If you have any questions, call Colette Jackson, Senior Regulatory Health Project Manager, at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Janet Maynard, M.D.
Cross-Disciplinary Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

JANET W MAYNARD
02/27/2015

Liu, Youbang

From: Liu, Youbang
Sent: Friday, January 09, 2015 6:00 PM
To: Thomas Moll <tmoll@adamispharma.com> (tmoll@adamispharma.com)
Cc: dcarlo@adamispharma.com
Subject: Information Request for NDA 207534, Quality

Dear Dr. Moll:

Please refer to your NDA 207534, dated May 28, 2014. We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests:

1. The (b) (4) method (b) (4) you submitted in the amendment has no detailed method description and validation results. A reference to a literature article for this analytical method is not sufficient. Provide detailed analytical method description and an adequate method validation report.
2. We have not been able to find the USP monograph methods referenced in the submission for "extractable volume" and "deliverable volume. Provide the USP monograph(s) used for the determination of both of these attributes or provide the detailed analytical method description and adequate method validation reports for both quality attributes.
3. Provide validation report for the sodium metabisulfite assay method.

Please acknowledge the receipt of this email and provide the amendment submission by January 20, 2015.

Regards,

Youbang Liu, Ph.D.
Regulatory Project Manager
Division III, ONDQA/OPS/CDER/FDA
10903 New Hampshire Avenue
Building 21, Room 2525
Silver Spring, MD 20903
Phone: (301) 796-1926



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II**

FACSIMILE TRANSMITTAL SHEET

DATE: November 21, 2014

To: Dennis J. Carol	From: Colette Jackson
Company: Adamis Pharmaceuticals Corp	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 858-461-0842	Fax number: 301-796-9718
Phone number: 858-412-7943	Phone number: 301-796-1230
Subject: NDA 207534 Epinephrine Injection- FDA Information Request	

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES xNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 207534
Adamis Pharmaceuticals Corporation
Epinephrine Injection USP (b) (4)

We refer to your May 23, 2014, NDA submission for Epinephrine Injection. We also refer to your November 17, 2014, email communication provided in response to our November 14, 2014, information request (IR) via email. We have the following comment.

We acknowledge your response to our IR of November 14, 2014. However, we disagree with your justification for the proposed deliverable volume (b) (4). The proposed product is a fixed-dose epinephrine drug-device combination product that is designed to be administered by a patient or caregiver in the unsupervised medical setting. In this setting, the maximum approved dose of epinephrine is 0.3 mg (b) (4). Modify the device so that it has a target deliverable volume of 0.30 mL and revise the associated specification acceptance criterion to a range of $0.30 \text{ mL} \pm (b) (4) \%$.

If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Drafted: Colette Jackson/November 20, 2014

Initialed: Sandy Barnes/ November 20, 2014
Peter Starke/ November 21, 2014
Janet Maynard/ November 21, 2014
Ying Wang/ November 21, 2014
Craig Bertha/ November 21, 2014
Julia Pinto/ November 21, 2014
Badrul Chowdhury/ November 21, 2014

Finalized: CCJ/ November 21, 2014

Filename: 207534 MO and CMC fax November 2014.doc

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

/s/

COLETTE C JACKSON
11/21/2014



NDA 207534

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Adamis Pharmaceuticals Corporation
11682 El Camino Real, Suite 100
San Diego, CA 92130

Attention: Dennis J. Carlo, Ph.D.
President and Chief Executive Officer

Dear Dr. Carlo:

Please refer to your New Drug Application (NDA) dated May 23, 2014, received May 28, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for epinephrine injection.

We also refer to your amendment dated June 18, 2014.

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 March 28, 2015.

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 February 28, 2015.

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 have the following comments and requests for information:

1. [REDACTED] (b) (4)
[REDACTED] List [REDACTED] (b) (4)
the drug product specification and propose an appropriate acceptance criterion. Express the assay value based only on [REDACTED] (b) (4) quantity.
2. Your proposed acceptance criterion [REDACTED] (b) (4) of [REDACTED] (b) (4) % is not acceptable. Your proposed limit is [REDACTED] (b) (4)
[REDACTED]
3. Propose an appropriate acceptance criterion for “total impurities” in the drug product that includes all identified and unidentified impurities, to help ensure the quality, purity, and potency of the drug product.

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](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

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.
2. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.
3. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

4. For drug products other than vaccines, the verbatim **bolded** statement must be present: **“To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch”**.
5. In the Table of Contents, all subsection headings must be indented and not bolded. The headings should be in title case.
6. The **bolded** section and subsection headings in the Full Prescribing Information (FPI) must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively).
7. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics*, in title case, and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.
8. The PATIENT COUNSELING SECTION of the FPI must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by August 29, 2014. 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:

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

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.

Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, call Colette Jackson, Senior Regulatory Health Project Manager, at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Lydia Gilbert-McClain, M.D.
Deputy Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Appendix A

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]

Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)]

[m/year]

[section (X.X)]

[m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

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

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

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

/s/

LYDIA I GILBERT MCCLAIN
08/06/2014



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: June 16, 2014

To: Dennis J. Carol	From: Colette Jackson
Company: Adamis Pharmaceuticals Corp	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 858-461-0842	Fax number: 301-796-9718
Phone number: 858-412-7943	Phone number: 301-796-1230
Subject: NDA 207534 Epinephrine Injection- FDA Information Request	

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES xNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 207534
Adamis Pharmaceuticals Corporation
Epinephrine Injection USP (b) (4)

Your application (NDA 207534) for Epinephrine Injection is currently under review. We have the following comment. Please provide the requested information by COB June 18, 2014, in order to facilitate our review of the application.

We note that your submission does not contain an integrated summary of efficacy (ISE) and integrated summary of safety (ISS), which are required by regulation to be submitted with the application. The ISE and ISS are detailed integrated analyses of all relevant data from clinical study reports. We also note that you have included summaries of efficacy and safety and provided links to the references in Module 5 within the Clinical Overview document in section 2.5. While we acknowledge that submission of a Clinical Overview is acceptable for this application, update Module 5 with an ISE and an ISS. The ISE and ISS may simply be short documents that refer to the information contained in the clinical overview document in section 2.5.

We also note that your submission does not contain section 2.7.3 (Summary of Clinical Efficacy) and section 2.7.4 (Summary of Clinical Safety). However, in contrast to the ISE and ISS, these summaries are optional.

If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Drafted: Colette Jackson/June 11, 2014

Initialed: Sandy Barnes/ June 12, 2014

Peter Starke/ June 13, 2014

Janet Maynard/ June 13, 2014

Finalized: CCJ/ June 16, 2014

Filename: 207534 MO fax 2014.doc

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

/s/

COLETTE C JACKSON
06/16/2014



NDA 207534

NDA ACKNOWLEDGMENT

Adamis Pharmaceuticals Corporation
11682 El Camino Real, Suite 100
San Diego, CA 92130

Attention: Dennis J. Carlo, Ph.D.
President and Chief Executive Officer

Dear Dr. Carlo:

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: Epinephrine Injection

Date of Application: May 23, 2014

Date of Receipt: May 28, 2014

Our Reference Number: NDA 207534

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 July 27, 2014, 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 Pulmonary, Allergy, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

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) 796-1230.

Sincerely,

{See appended electronic signature page}

Colette Jackson
Senior Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

COLETTE C JACKSON
06/06/2014