APPLICATION NUMBER:

207534Orig1s000

OTHER ACTION LETTERS
Dear Dr. Carlo:


We acknowledge receipt of your amendment dated December 4, 2015, which constituted a complete response to our March 27, 2015, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

**CLINICAL**

You have not submitted adequate data to support the safe and effective use of Symjepi (epinephrine) prefilled syringe for the emergency treatment of allergic reactions (Type I) including anaphylaxis. Specifically, the data from your human factors and usability assessment study raise concerns that the product as designed will not be safe and effective for the intended users, and use environments. We note the following deficiencies:

1. There were limitations in the conduct of the submitted study, such as inadequate representation of various user groups (such as adult subjects, adolescent subjects, trained subjects, trained subjects with adequate elapsed time between training and study to account for decay of memory, untrained subjects, subjects with prior experience with epinephrine autoinjector, subjects naïve to epinephrine autoinjector, etc.), and use environments (such as simulated emergent situation with distractions and loud noises). Furthermore, in your submitted study, approximately 75-85% of the participants were trained by video or written material or both, which is likely not reflective of the actual use scenario for your proposed product.

2. The limitations in the conduct of the submitted study notwithstanding, the results demonstrate an unacceptably high failure rate in performances of critical tasks that could result in serious harm because with these errors the users may not get the intended dose.

Reference ID: 3941301
of epinephrine. Failures in critical tasks elements that rendered the product incapable of delivering the injection included: failure to remove the needle cap and/or premature deployment of the needle guard (n = 3 [4%]) and premature depression of the plunger (n = 2 [3%]). One participant had difficulty with removing the needle cap and pulled the needle cap off at an angle which resulted in the needle cap rim catching the safety guard lip and prematurely deploying the needle guard resulting in the device locking and no injection being delivered.

INFORMATION NEEDED TO RESOLVE DEFICIENCY

To support approval of Symjepi Prefilled Syringe for the emergency treatment of allergic reactions (Type I) including anaphylaxis you will need to provide adequate data to support the safe and effective use of your product in this emergent life-threatening situation. This deficiency may be addressed as follows:

Conduct a human factors and usability assessment program that includes formative evaluation, and human factor validation testing with adequate representation of user groups and use environments as mentioned above. The extent of the training that participants receive should approximate the training that actual users would receive. Include clear brief step wise instruction of critical elements on the device, each of which is tested as part of the formative and validation studies. Depending on the findings of these studies, device changes may become necessary, because modifying the device design is usually more effective that revising the labeling or training. We acknowledge that even if best practices were followed in the design of the user interface, it may not be possible to make a device error-proof or risk-free. All risks that remain after human factor validation testing should be thoroughly analyzed to determine whether they can be reduced or eliminated. We recommend that you submit all protocols for human factors validation for our review and recommendations prior to conducting the validation study. Refer to the guidance for industry “Applying Human Factors and Usability Engineering to Human Devices” available at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf for guidance on conducting the human factors assessment program.

In addition, we have the following comments.

1. 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 +/- % of drug over the 18-month expected use life with a % reliability and % 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 [redacted].

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.

2. In your response to the sharps injury prevention question, you provided testing of a sample size [redacted] with zero failures. 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 an adequate scientific rationale [redacted].

3. In your response regarding biocompatibility testing [redacted], dated May 3, 2016 you state, “that in view of the anticipated duration of the proposed studies [redacted] proposes to conduct and report the biocompatibility tests summarized in Table 3 [redacted].” 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.

**PRESCRIBING INFORMATION**

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm) website including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances. Your response must include updated 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](http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm).

**PROPRIETARY NAME**

Please refer to correspondence dated, May 6, 2016, which addresses the proposed proprietary name, Symjepi. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

**SAFETY UPDATE**

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

**OTHER**

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, “Formal Meetings Between FDA and Sponsors or Applicants,” May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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
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
06/03/2016
NDA 207534

COMPLETE RESPONSE

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 acknowledge receipt of your amendments dated June 18, August 26, October 8, November 27, and December 12, 2014, and January 20, and February 6, 13, and 19, 2015.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

1. The deliverable volume of the drug product is a critical quality attribute for this drug for its intended use and use environment. The drug/device combination product as submitted in the application is not capable of delivering the labeling claim amount of the drug. This will not ensure the identity, strength, quality, purity, and potency of the drug product per CFR 314.50(ii)(a).

You need to redesign the pre-filled syringe to deliver the target volume at labeling claim. In your future submission you need to provide the following:

i) Detailed device information with the original design and redesign comparison

ii) Detailed validation report with the redesigned device performance data. It should include but not limited to; sample size, average deliverable volume, standard deviation, minimum and maximum volume delivered, etc.

iii) Detailed validation batch (with the intended drug product solution) data with the redesigned device
You need to propose an acceptance criterion for the “deliverable volume” with reasonable lower and upper limits that is comparable to the limits of other approved drug products in this class. Please note the proposed acceptance criterion for “mean deliverable volume” with limit in the footnote (as in your amendment dated Feb 6, 2015) is not appropriate or adequate.

2. The volume determination as described in USP <1> is not specifically defined for which type of the volume. The is irrelevant regarding the analytical methods for the extractable volume for this pre-filled syringe to be used by the patients. You need to provide detailed analytical methods and adequate validation report for the extractable volume of the drug product.

3. Your proposed drug substance specification (Table 3.2.S.4.1-1) in the NDA is looser than that used by the drug substance supplier referenced in DMF. Specifically,

   i) The proposed acceptance criterion for impurity is in your NDA submission. The acceptance criterion for this impurity is %.

   ii) There is residual solvent limit of ppm in the specification. However, this limit is not in the drug substance specification proposed in the NDA.

   Revise your specification to match the specification of the drug substance supplier. Accordingly you also need to provide an appropriate analytical method and adequate validation report for the impurity. Please note a limit test for any impurity is not acceptable. Alternately, provide justification to support your proposed specification (or lack of such specification). Please note that merely following the USP monograph is not sufficient justification for any impurity limit. ICH Q3A guideline also needs to be followed. Any potential residual solvent in the drug substance needs to be specifically listed and limit be set in the specification. Statement of is not sufficient.

**PREScribing INFORMATION**

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the website including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances. Your response must include updated 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](http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm).
PROPRIETARY NAME
Please refer to correspondence dated, March 2, 2015, which addresses the proposed proprietary name, Symjepi. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE
When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

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OTHER
Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, “Formal Meetings Between the FDA and Sponsors or Applicants,” May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

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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
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
03/27/2015