CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205920Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205920

COMPLETE RESPONSE

Armstrong Pharmaceuticals, Inc.
Attention: Gisela Sharp
Senior Manager, Regulatory Affairs
11570 6th Street
Rancho Cucamonga, CA 91730

Dear Ms. Sharp:

Please refer to your New Drug Application (NDA) dated July 20, 2013, received July 22, 2013, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Primatene Mist (epinephrine inhalation aerosol), 125 mcg per spray.

We acknowledge receipt of your amendment dated June 28, 2016, which constituted a complete response to our May 22, 2014, 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

Although we believe that you have made significant improvement to the user interface, the results from your consumer studies do not support the proposed over-the-counter (OTC) use of epinephrine hydrofluoroalkane (HFA) inhalation aerosol for the temporary relief of mild symptoms of intermittent asthma in adults and adolescents 12 years of age and older.

Specifically, the human factors (HF) study (G3) failed to demonstrate that the user interface supports safe and effective use of the product by intended users for the proposed uses in the OTC setting. In your analysis of the HF data, you considered participants coded as completed (C) and completed with issues (CI) as having successfully completed the three primary tasks in the HF study. We do not agree with this analysis and consider some of the participants coded CI as failures. For participants coded as CI, correct use after encouragement by the moderator to refer back to the label does not mitigate the initial error. We have conducted further mitigation analysis based on the results from your bench studies to determine whether the errors were clinically relevant.

Based on our mitigation analysis of the data you provided, we conclude that approximately 30% of participants in the HF study failed at least one of the three primary tasks (critical use tasks) of the study: initial priming of the inhaler (Task 1), cleaning of the inhaler (Task 2), or routine use (re-priming) of the inhaler (Task 3). Our analysis for Task 1, Task 2 and Task 3 found 13%,

12%, and 13% of participants had errors that could lead to clinically important under or supra-therapeutic dosing. Because some participants had clinically important errors in more than one task, this yields 30% of participants with an error for at least one task. This is an important clinical concern because, if these tasks are not correctly performed, users of this product will not reliably receive the correct dose and may either under-dose, which will likely result in lack of efficacy, or receive a supra-therapeutic dose. If users do not obtain relief with the inhaler they will view the product as ineffective.

Information Needed to Address Deficiency:

To address the deficiency, you may consider developing an alternative inhalation device and testing it anew. Alternatively, you may choose to maintain the existing device and further optimize the labeling to improve consumer understanding and ability to complete the use tasks of priming, cleaning, and routine use (re-priming) (the first 3 objectives of the HF study).

We have already provided a number of recommended changes that have been adopted in the Drug Facts labeling (DFL), the consumer information leaflet (CIL), and the outer carton. We also recommend further changes to the labeling regarding the mouthpiece instructions, including:

1. making the embossed instructions on the mouthpiece more legible, such as by increased contrast between the font and the background

2. aligning the instructional language on the actuator to the revised DFL and CIL

3. adding pictograms, for key steps, to the mouthpiece. This could provide an additional prompt to consumers about correct use when they are having an asthma attack.

You may also consider other approaches to optimizing consumer understanding and use of the device.
We recommend that you re-evaluate the primary task failures and difficulties and their associated root causes, update your risk analysis accordingly, and implement additional risk mitigation strategies as needed. Conduct another HF validation study after you implement all changes. Consider designing your protocol to include retesting subjects several weeks after the initial test session to simulate intermittent use.

In your HF validation study, assess consumers' ability to use the epinephrine HFA inhalation aerosol and include the three primary tasks (critical tasks) from the G3 study: initial priming of the inhaler, cleaning of the inhaler to prevent clogging, and routine use (re-priming) of the inhaler. Note that HF validation testing should include at least 15 participants from each distinct user group. Ensure that you have adequate representation of subjects with low literacy, adolescents, subjects with asthma, and subjects with previous inhaler experience. Additionally, when demonstrating that your product can be used safely and effectively, we note that any prompting or cues by study moderators during the validation study is not reflective of the real life OTC use scenario or environment for your proposed OTC product. Therefore, the interviewer should not mention that this product "may work differently than the one you are used to or may have used in the past."

We recommend you submit your HF validation study protocol for our review and comment prior to conducting your HF validation study. Additionally, a community-based actual use study evaluating reports of device complaints or issues and characterizing sources of error may be helpful.

We note that in G3 for the 145/151 participants for which a HF video was available, the device was not assembled (i.e., canister was not secured in the actuator) for five, or 3.4% (5/145) of study participants. You have stated that all were able to effectively reposition the canister into the actuator, and concluded that in any case this separation was an artifact of Study G3 and will not occur with the commercial product. In your HF validation study protocol, discuss how you will address this issue, and in the HF validation study report, provide corresponding data on how many devices were disassembled in some way upon opening and how many subjects were capable of reassembling on their own, with the time to reassemble documented for each subject.

The requested information should be placed in eCTD section 5.3.5.4 – Other Study reports and related information.

Guidance on human factors procedures to follow can be found in:
Applying Human Factors and Usability Engineering to Medical Devices, available online at:
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf

Guidance on Safety Considerations for Product Design to Minimize Medication Errors, available online at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf

Note that we recently published two draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling:

Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development, available online at:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM484345.pdf

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, available online at:
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

ADDITIONAL COMMENTS

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling revised as follows:

Changes to the outer carton outside Drug Facts:

1. The lot number and expiration date must be visible on the immediate and outer containers, in accordance with 21 CFR 201.17 and 201.18.

2. [redacted] (b) (4) Revise the statement of identity as noted in the November 22, 2016 information request:

   Epinephrine Inhalation Aerosol
   0.125 mg per spray
   Bronchodilator

   Use bold type and white font so the text can be readily perceived on the PDP given the background is dark brown.

3. Revise the "Shake [redacted] (b) (4) Spray into the air before each inhalation" statement on the PDP as follows:

   Suspension:
   Shake [redacted] (b) (4) Spray
   into air before
   each inhalation

Changes to the outer carton Drug Facts labeling (DFL)

1. The Drug Facts labeling did not include the barlines and hairlines required by 21 CFR 201.66(d)(8). Refer to 201 CFR 201.66(d)(8) and 21 CFR Appendix A to Part 201 for formatting information in Drugs Facts. An example of a standard labeling format with the required barlines and hairlines can be seen in 21 CFR Appendix A to Part 201.
2. Provide complete Drug Facts font specifications. See 21 CFR 201.66(d) and guidance for industry – Labeling OTC Human Drug Products (Small Entity Compliance Guide) May 2009.
3. Under the asthma alert, remove the bullet in front of the statement "These may be signs that your asthma is getting worse". Add a period at the end of the statement per 21 CFR 341.76(c)(6)(F).

4. Under **Directions** in the DFL, include the following instruction for washing the mouthpiece: [redacted]

Changes to the immediate container label

1. [redacted]

2. The statement of identity reads, Epinephrine Inhalation Aerosol [redacted] Revise the text to be black font and bolded, and edit the statement of identity as follows:

   Epinephrine Inhalation Aerosol
   0.125 mg per spray
   Bronchodilator

3. In the Active Ingredient heading, in parenthesis it states [redacted] Revise the statement to read "in each spray."

4. Under **Directions** in the DFL, include the statement [redacted]

5. There is a Warning statement to [redacted]

Changes to the consumer information insert

1. Under section B. [redacted]

2. Under section C. [redacted]

Changes to the website

1. We recommend that the videos on your website be revised to be consistent with the DFL/CIL and that you add the statement, "see www.primatene.com" to the CIL.

2. On the first webpage for the website, (b) (4) was added to the statement of identity. Delete (b) (4) from the statement of identity.

3. On the DFL page, under the asthma alert, there is a bullet in front of the statement "These may be signs that your asthma is getting worse." Remove the bullet and place a period at the end of the statement.

4. Under **Directions** in the DFL, include the following instruction for washing the mouthpiece: (b) (4)

5. Ensure the text on the website is consistent with the language recommended on the PDP, the Drug Facts labeling for the outer container, and the consumer information leaflet.

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/product 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 in the original submission.
   - Present tabulations of the new safety data combined with the original/supplemental application data.
   - Include tables that compare frequencies of adverse events in the original /supplemental application 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/supplemental application data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

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. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. 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 draft FDA guidance for industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," March 2015 at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.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 Tinya Sensie, Regulatory Project Manager, at (240) 402-4230.

Sincerely,

{See appended electronic signature page}

Theresa Michele, MD
Director
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
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/

THERESA M MICHELE
12/23/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205920

COMPLETE RESPONSE

Armstrong Pharmaceuticals
Attention: Stephen A. Campbell, Esq.
Sr. Vice President, Regulatory Affairs
25 John Road
Canton, MA 02021

Dear Mr. Campbell:

Please refer to your New Drug Application (NDA) dated July 20, 2013, received July 22, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Epinephrine HFA Inhalation Aerosol 125 mcg/actuation.

We also acknowledge receipt of your amendments dated: September 10, 16, and 19, November 5 (three), December 4 (three), 11, 20, and 23, 2013, January 14 (two), 27 (three), and 30, February 5, 6, 21, 22 and 28, March 18, 19, 24, and 26, April 2, 7, 9, 13, 16, 18 and 21, and May 12, 2014.

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

During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed current Good Manufacturing Practices (cGMP) deficiencies to the representative of the facility.

Information needed to address deficiency
Satisfactory resolution of these cGMP deficiencies is required before this application may be approved.

NONCLINICAL

The proposed epinephrine HFA inhalation aerosol includes thymol, which is not a qualified excipient for oral inhalation products intended for chronic use.

Information needed to address deficiency
Provide information supporting the safety of chronic inhalation of thymol. If such information is not currently available, conduct a repeated dose inhalation toxicity study of 6 months duration in

an appropriate species that shows no adverse findings to support the use of thymol in your product.

CLINICAL

The submitted data do not support the proposed over-the-counter (OTC) use of epinephrine HFA inhalation aerosol for the temporary relief of mild symptoms of intermittent asthma in adults and adolescents 12 years of age and older.

The data from patient diaries and assessment of device and dose indicator performance in your clinical trials indicate that consumers may have difficulty using the proposed product correctly. Specifically, patients reported a high number of device malfunctions in your phase 3 clinical trials. One third of the reports (clogging and not dispensing properly) raise concerns regarding potential clogging. Your analysis identified user error as the potential cause for the reports of malfunction. User error with the dose indicator also appears to have contributed to patients' perception of device malfunction. Usability issues are a significant concern for an OTC inhaler product used to treat acute asthma symptoms.

The data from your behavioral study do not provide assurance that consumers clearly understand how to use epinephrine HFA inhalation aerosol. Your behavioral study did not assess whether consumers understood the need to initially prime and clean the product without prompting. It was difficult to assess whether cleaning of the device was performed appropriately as some subjects had difficulty demonstrating the cleaning steps without a sink. Some consumers had difficulty removing the canister to clean the product, and the study did not assess whether consumers correctly reassembled the product after cleaning. In addition, your behavioral study did not adequately assess consumers with low literacy.

Your label comprehension studies identified limitations in consumers' understanding of the following critical information: relying on the indicator if dropped, the need to prime the inhaler before using the first time, the need to clean the product daily after use, and the need to reprime when wet.

We note the complexity of the steps required for shaking, priming, actuation, and cleaning in order to ensure adequate product performance. The issues described above raise concerns about consumers' ability to use your epinephrine HFA inhalation aerosol product for the acute treatment of asthma in the OTC setting. This usability issue is concerning for an OTC product because consumers will be using the device without the oversight of a health care professional (who the user might call if there is a problem).

Information needed to address deficiency
To support approval of epinephrine HFA inhalation aerosol, you must provide data to support consumers' ability to use epinephrine HFA inhalation aerosol in the OTC setting, including the aspects of such use discussed above. To accomplish this you will need to do the following:

1. Revise the labeling to optimize comprehension and assess the revised label in a label comprehension study. Optimize the labeling to improve comprehension of the following critical information: prime before first use of the product, clean the product on each day of use, reprime the inhaler when wet, do not rely on the dose indicator if dropped, instructions on removing the canister for cleaning and proper reassembly, press on the center of the dose indicator, and orientation of product during use and storage.

2. Conduct a behavioral (human factors) study with the revised label using the actual product (not a dummy product) to assess consumers' ability to use epinephrine HFA inhalation aerosol. Include sufficient numbers of consumers with low literacy in your population assessed against target thresholds; ideally this population should be representative of the proportion of adults in the United States with basic literacy skills based on available national data. Include a sink so consumers have to demonstrate appropriate cleaning steps. Consumers should not be prompted on specific steps. Based upon the findings of the behavioral study, further changes to the label or the device may be necessary and additional behavioral (human factor) study(ies) may be necessary.

3. After conducting smaller behavioral (human factor) study(ies) to refine the labeling and potentially the device, conduct a randomized, actual use study with the revised labeling and proposed epinephrine HFA inhalation aerosol to rigorously quantify and evaluate complaints or problems associated with use of the product and characterize sources of user error. Assessment of patient complaints or problems with the dose indicator should be included in this study. We strongly recommend that you include a marketed bronchodilator product as a benchmark comparison in the study.

Depending on the results of the above iterative evaluations, modification of the product and product labeling may be necessary to minimize potential user error, e.g., revised patient instructions for use, replacement of the current dose indicator with an integrated dose counter, product reformulation and product change to simplify the steps required for adequate product performance, etc. Changes to the product may necessitate additional *in vitro* or clinical data for support.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21CFR314.50(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).

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

1. We recommend that you incorporate acceptance criteria for accuracy into the dose indicator specification. Propose a sampling plan and acceptance quality limit (AQL), for example, (b) (4) % for regular inspection, for dose counter accuracy testing.

2. We recommend that you revise the Directions section of the Drug Facts Label to state "Children under 12 years of age: Do not use; it is not known if the drug works or is safe in children under 12."

3. Members of the Advisory Committee raised the issue of whether this product will be misused in consumers with asthma resulting in adverse asthma outcomes. Consider whether elements of your product or labeling could be modified to address this issue. If modifications are made, include these as test elements in label comprehension and actual use studies.

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. We also encourage you to request FDA advice regarding protocol designs prior to embarking on consumer studies.

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 Daniel Reed, Regulatory Project Manager, at (301) 796- 2220.

Sincerely,

{See appended electronic signature page}

Theresa Michele, M.D.
Director
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ENCLOSURE:
None

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

/s/

THERESA M MICHELE
05/22/2014