# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 208437Orig1s000

# OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208437

**COMPLETE RESPONSE**

Sunovion Respiratory Development Inc.
84 Waterford Drive
Marlborough, MA 01752-7010

Attention: Renee M. Carroll, MS, RAC
Senior Director, Regulatory Affairs

Dear Ms. Carroll:

Please refer to your New Drug Application (NDA) dated July 28, 2016, received July 29, 2016, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Glycopyrrolate Inhalation Solution, 25 mcg/mL.

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.

The following comments pertain to PARI eFlow Closed System nebulizer:

1. In your response to the Information Request dated, March 17, 2017, you provided two new chemical extractable and leachable (E&L) tests for the eFlow Closed System Nebulizer . Both tests were conducted using water as the polar extraction solvent and isopropanol (IPA) as the non-polar solvent. The extraction conditions used were identified as 50°C for 72 hours or 60°C under sonication for up to 24 hours. In the test reports provided, you stated that IPA used as the non-polar extraction solvent caused significant degradation of the test devices, under both of the two extraction conditions.

   The eFlow Closed System Nebulizer proposed is indicated for permanent use. In clinical use, the device will come into direct contact with the SUN-101 (glycopyrrolate) Inhalation Solution and patient's exhaled gases. When being exposed to such clinical conditions, both polar and non-polar chemical residues may potentially leach out from the device, which may pose significant health risks to patients when inhaled.

   As the IPA extraction solvent was demonstrated to be incompatible with the test device materials and caused device degradation, the test data from the IPA extracts are considered invalid. Thus your E&L testing provided is considered inadequate for the biocompatibility endpoints assessments for systemic toxicity and genotoxicity and inadequate to address the drug-device material compatibility.

   To address the safety concerns for the eFlow Closed System Nebulizer,

provide a revised chemical E&L testing at 50°C for 72 hours, using an appropriate non-polar extraction solvent that is compatible with the test device and does not cause the device degradation. We recommend that you use a non-polar extraction solvent or a mixed solvent system that is chemically similar in polarity to the intended medications. Alternatively, you may provide the revised chemical testing based on the intended drugs or a surrogate chemical that has chemical properties similar to the drugs proposed. If a surrogate or non-polar solvent was used, provide your scientific rationale and justification for your choice of the surrogate or the non-polar solvent to demonstrate that the worst clinical use condition is represented. In addition, clarify whether the surrogate or solvent used compromises the integrity of the tested device or representative component samples.

Provide a revised toxicological risk assessment (exposure and safety assessment) for all chemical compounds identified from the revised E&L testing, including organics, inorganics, organometallics, metals, and other residues. To address a worst case safety concern, the maximum amounts of the chemicals identified per device system should be considered in the risk assessment calculation. The risk assessment calculation should also take into consideration the inhalation exposure route, intended patient population, and a worst case scenario. For analysis of the chemical residues and the allowable limits, refer to the published toxicological literature for the reference doses, such as the no observed-adverse-effect-levels (NOAELs) and lowest-observed-adverse-effect levels (LOAELs), and/or to the inhalation protective values from the US based health organizations or WHO. For the risk assessment calculation, you may also refer to the FDA-recognized standard ISO 10993-17:2002(R)2012 Biological evaluation of medical devices - Part 17: Establishment of allowable limits for leachable substances, and the TTC approaches described in the CDER ICH M7 guidance. Clearly identify the calculated margin of safety (MOS) value for each of the chemicals identified and describe in detail (step-by-step) how the MOS values were calculated. Provide a clear rationale for the uncertainty values that are used in the exposure and safety assessment for each chemical residue.

Be advised, if a safety signal (e.g. chemicals with MOS <1) is identified through your risk assessment of the chemical extractables and leachables, additional justification or biological testing may be warranted in order to address this risk.

## 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* and *Pregnancy and Lactation Labeling Final Rule* websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information 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

## PROPRIETARY NAME

Please refer to correspondence dated, August 25, 2017, which addresses the proposed proprietary name, Lonhala Magnair. 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 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 application data.
    - Include tables that compare frequencies of adverse events in the original 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 application 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 product. Include an updated estimate of use for product 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 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 Sadaf Nabavian, Regulatory Project Manager, at (301) 796-2777.

Sincerely,

*{See appended electronic signature page}*

Lydia Gilbert-McClain, MD
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
05/26/2017