

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**214375Orig1s000**

**OTHER ACTION LETTERS**



NDA 214375

**COMPLETE RESPONSE**

Polarean Inc.  
Attention: Jason Mercer, PhD, RAC  
Authorized US Agent  
Product Development Champion  
c/o Facet Life Sciences  
215 E Deer Run  
Durham, NC 27523

Dear Dr. Mercer,

Please refer to your new drug application (NDA) dated October 5, 2020, received October 5, 2020, and your amendments, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Xenoview (xenon-129 hyperpolarized) for Inhalation.

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**

The Approvability Issues (deficiencies), with recommendations to address them, are as follows:

**A. Drug Substance and Drug Product**

1. The degree of polarization of xenon-129 hyperpolarized is a critical quality attribute of the drug component in your drug-device combination product. Establish specification and acceptance limits with tolerances (acceptable variation) with adequate justification per 21 CFR 314.50(d)(ii)(a). Include measurements from clinical batches of xenon-129 hyperpolarized produced by the device (b) (4) and proposed commercial batches produced by (b) (4). Submit a table with batch results, batch identification number/date, and batch use (e.g., health center-clinical, registration, etc.).
2. Validate the production method of xenon-129 hyperpolarized using at least three different batches of gas blend (b) (4) on (b) (4) commercial hyperpolarizer (b) (4). The

registration batches of xenon-129 hyperpolarized must meet final drug specification and be produced according to the proposed regulatory commercial production process under cGMP with documented actual yield and % of theoretical yield. This is a requirement under 21 CFR Part 4 if adopting the streamlined approach and implementing 21 CFR Part 820 regulations as the quality system. Submit to the application the master batch record and executed batch records for production of xenon-129 hyperpolarized from hyperpolarizer (b) (4) manufactured (b) (4) (b) (4)

3. Propose a strength for the drug product xenon-129 hyperpolarized, e.g., range of percent xenon-129 enrichment and range of percent hyperpolarization per volume.

#### **B. Device Design Changes and Release**

4. Provide the final approval procedure along with approved release documents that will be reviewed and approved by Polarean for release of the finished devices (b) (4)
5. Provide a comparative list of all the changes (b) (4) of the Hyperpolarizer and provide verification protocol/testing data for each of the changes to support the design changes. Provide detailed description for the (b) (4) change (b) (4) along with its material characteristics and its comparative analysis with the (b) (4) used for clinical studies.

#### **C. Device Reliability**

6. You have failed to provide reliability assessment reports for the Hyperpolarizer and the QC Measurement system. Submit the verification protocol, analytical tests/ methods, specifications and acceptance criteria, and final report for review and approval to support the annual calibration period and any proposed recertifications.

### **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 Prescription Drug Labeling Resources<sup>1</sup> and Pregnancy and Lactation Labeling Final

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<sup>1</sup> <https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources>

Rule<sup>2</sup> 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 FDA.gov.<sup>3</sup>

### **CARTON AND CONTAINER LABELING**

We reserve comment on the proposed labeling until the application is otherwise adequate.

### **PROPRIETARY NAME**

Please refer to correspondence dated, December 29, 2020, which addresses the proposed proprietary name, **Xenoview**. 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.

### **FACILITY INSPECTIONS**

During a recent inspection of the Polarean Inc. (FEI:3010132318) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

During a recent inspection of the [REDACTED] (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

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### **SAFETY UPDATE**

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<sup>2</sup> <https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule>

<sup>3</sup> <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

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 guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

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 Lisa Skarupa, Regulatory Project Manager, at 301-796-2219.

Sincerely,

*{See appended electronic signature page}*

Charles Ganley, M.D.  
Director  
Office of Specialty Medicine  
Office of New Drugs  
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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CHARLES J GANLEY  
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