DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209607

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

Progenics Pharmaceuticals, Inc.
Attention: Jouliana Jean-Paul, J.D.
Regulatory Affairs Manager
1 World Trade Center
47th Floor, Suite J
New York, NY 10007

Dear Ms. Jean-Paul:

Please refer to your New Drug Application (NDA) dated October 31, 2017, received October 31, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Azedra (131I-Iobenguane) solution for intravenous use.

We also refer to your amendment dated December 15, 2017.

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 **Priority**. Therefore, the user fee goal date is April 30, 2018.

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 requirement/commitment requests by March 30, 2018.

During our filing review of your application, we identified the following potential review issues:

Drug Substance

1. Provide 12 months' long-term stability data for the three registration batches of the Drug Substance precursor.

Microbiology

2. We acknowledge the information provided in Module 3.2.P.2 regarding container closure integrity testing. However further information is required to assess the acceptability of the container closure integrity testing methods.

   a. Describe the controls used for the study and provide results for the controls.

   b. Clarify if the test units were exposed to the proposed storage temperature (-70 °C). If not, provide a scientific rationale for not performing this step. Alternatively, provide a study representative of the proposed storage protocol.

3. A reprocessing statement cannot be located. Please indicate whether reprocessing of the drug product is allowed.

4. We acknowledge the information provided in Module 3.2.A.1 regarding the environmental monitoring program. Additional information is required, however, to assess the acceptability of the proposed environmental monitoring program.

   a. Provide alert and action limits for air, surfaces, and personnel.

   b. Describe the monitoring program for water for injection.

   c. Provide the pre-filtration bioburden limit for the bulk drug product.

   d. Specify the actions taken when limits are exceeded.

   Refer to the 1994 Agency Guidance for Industry on Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products.

5. We acknowledge the information provided in Module 3.2.P.3.3 regarding the sterilization of the sterilizing filter and filling components. The submission states that the sterile processing components (sterilizing filters, syringe, needles, manifolds, tubing, adaptors, and bags) are purchased pre-sterilized (Description of Manufacturing Process and Process Controls, page 10 of 10; Process Validation and/or Evaluation, page 12 of 63). Provide complete validation studies in support of the sterilization process for the sterilizing filter and filling components or, if applicable, a letter of authorization for a DMF that references the submission date and location of the appropriate studies and data.

6. We acknowledge the information provided in Module 3.2.P.7 regarding the sterilization and depyrogenation of the containers and closures. The submission states that the vials are purchased ready-to-use from Acorn Industries. The referenced DMF 14106 from

Gerresheimer does not contain information regarding the vial sterilization/depyrogenation process. Provide a letter of authorization for a DMF that references the submission date and location of the appropriate vial sterilization/depyrogenation studies and data.

7. We acknowledge the information provided in Module 3.2.A.1 regarding the decontamination of the hot cell using vaporized hydrogen peroxide (VHP). Provide complete validation studies in support of the VHP decontamination process.

8. We acknowledge that three consecutive media fills were performed at the Zevacor facility (Process Validation and/or Evaluation, page 6 of 63). Please submit the following:

   a. A complete description of the media fill procedures and specifications.

   b. Results from the three consecutive media fill runs, including growth promotion testing and environmental monitoring.

   c. A description of the actions taken after media fill failure.

9. We acknowledge the information provided in Module 3.2.P.5 regarding the endotoxins testing method. Indicate the dilution that will be used for routine testing.

Please submit your response to these items by January 16, 2018.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

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. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances; and,

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Labeling issues and comments identified during our preliminary review of your submitted labeling are attached.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by January 12, 2018. 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. The checklist is available at the following link: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM373025.pdf.

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:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the 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 the drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, please call Sharon Sickafuse, Senior Regulatory Health Project Manager, at (301) 796-2320.

Sincerely,

{See appended electronic signature page}

Steven Lemery, M.D.
Associate Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
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/

JOSEPH E GOOTENBERG on behalf of STEVEN J LEMERY
12/28/2017