CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202158Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202158

COMPLETE RESPONSE

NorthStar Medical Radioisotopes, LLC
Attention: Scott D. Moffatt
Vice President of Regulatory Affairs and Quality
5249 Femrite Rd.
Madison, WI 53718

Dear Mr. Moffatt:

Please refer to your New Drug Application (NDA) dated January 4, 2013, received January 4, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for TechneGen Generator System for Preparation of Sodium Pertechnetate Tc99m Injection, (Sodium Pertechnetate Tc99m Injection USP) Injection, (b) (4)

We acknowledge receipt of your amendments dated January 18, 22, 23, and 28, February 15, March 1, April 1, 17, and 24, May 15, June 21, July 9, and September 12, 2013.

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

There are multiple deficiencies in the product labeling, including the user manuals, training materials and package insert related to instructions for preparation and safe use of the TechneGen system. These deficiencies have prevented the full evaluation of the safety of the TechneGen generator system. Please refer to the meeting minutes from our teleconference on July 17, 2013, for a detailed discussion of these issues and for our recommendations on how to revise the user manuals and training materials and how to design and conduct a human factor testing study to provide meaningful data to support the safe use of the generator.

PRODUCT QUALITY MICROBIOLOGY

1. At this time, the safety of the TechneGen cannot be evaluated from a microbiological perspective because the NDA does not contain sufficient data to determine whether the proposed system can provide the expected sterility assurance level.

2. The application lacks data sufficient to support the ability of the proposed TechneGen system to remain in a state of microbiological control over the (b) (4) in-use period.

You will need to demonstrate that the tubing, valves, and connectors may be used as described without increased risk of microbial contamination/proliferation within the non-sterile manufacturing system. You will need to address the risk of biofilm formation on the tubing and in the valves. The valves are highly unlikely to be dried completely with the (b) (4) and this seems consistent with your observation that the tubing connections can retain liquid droplets after (b) (4). Additionally, you will need to address the risks posed by the possibility of leaking connections and encrusted connections cited in the labeling, and develop a procedure required to assess and correct these malfunctions.

3. The application lacks data sufficient to support the claim that the TechneGen system is a (b) (4) process. This claim is used to justify proposed deviations from industry best practices and it is an unsubstantiated claim. You will need to provide the data that demonstrate this is a (b) (4) process.

4. The cleaning protocol has not been validated to remove contaminating organisms from the TechneGen system. You will need to provide data that demonstrate the proposed cleaning protocol is adequate to maintain microbiological control of the system.

5. There is no confirmation that the final patient dosage form has been sterilized. The sterilizing filter should be integrity tested prior to release of the drug product. You will need to describe the test method and acceptance criteria in the application and the labeling. The user should be provided with information on what to do if the integrity test fails.

6. The process validation studies conducted to date are not adequate to support the proposed manufacturing process. There will be no aseptic processing simulations conducted by the end user and thus there will be no confirmation that the user is capable of safely preparing a sterile dosage form. You will need to justify this deviation from industry best practice.

7. Please provide the English translation of appendix 1, 2, 4, 6, 7, 8, 9, and 15 to the (b) (4) sterilization validation report 77C01891.

8. Please provide a description of (b) (4) 1320 and 1516 used at (b) (4)

9. Please provide the following information on the manufacture of the (b) (4) in (b) (4) vials.
   a. A brief summary of the environmental monitoring program to include the manufacturing room classifications
   b. The proposed (b) (4) for commercial use
   c. The methods and controls used to monitor production (b) (4)
   d. Indicate whether reprocessing is allowed

e. Justify the [(b) (4)] acceptance criteria for validation studies based solely on the [(b) (4)] and the lack of acceptance criteria for [(b) (4)].
f. Provide a description of the [(b) (4)] used during validation studies #2, 3, and 4

10. Please provide the following information on the manufacture of the 1.5M sodium acetate in [(b) (4)] vials and the 3% H_2O_2 in [(b) (4)] vials.
    a. A brief summary of the environmental monitoring program to include the manufacturing room classifications
    b. Justify the proposed bracketing approach for the [(b) (4)] validation studies. [(b) (4)].
    c. The proposed [(b) (4)] for commercial use
    d. The methods and controls used to monitor production loads
    e. Indicate whether reprocessing is allowed
    f. Justify the [(b) (4)] acceptance criteria for validation studies based solely on the [(b) (4)] and the lack of acceptance criteria for [(b) (4)].
    g. Provide a description of the [(b) (4)] used during the 4 validation studies described in reports JN11F0412 and JN12I0706
    h. Explain how the submitted validation studies are applicable to the [(b) (4)] vials intended for commercial runs

11. Please provide the sterilization validation information for [(b) (4)] supplied by [(b) (4)] (product # [(b) (4)]) and [(b) (4)] (product [(b) (4)]. The information submitted in document 09-001 from [(b) (4)] does not indicate that these two suppliers are covered by the submitted validation studies.

12. As requested in the filing communication, please provide the [(b) (4)] sterilization validation studies for the [(b) (4)] and [(b) (4)] 0.22 µm sterilizing filters. Your inclusion of a copy of the label is not sufficient. Alternately, provide a letter of authorization to a DMF or reference to a 510k that contains this information. The letter of authorization should clearly indicate where in the DMF the information is located.

13. The proposal to [(b) (4)] has not been justified with appropriate data to insure that the final patient dosage form will meet the proposed specification. No data are available to define the routine bioburden or endotoxin present in the manufacturing environment [(b) (4)] USP<85> requires that radiopharmaceutical products contain <175 EU/dose to insure patient safety. Assuming a worst-case elution, the final 7 mL should contain NMT 25 EU/mL. You will need to indicate how this level of endotoxin content in the final eluted drug product will be assured.

14. Please explain why the protocol and report for 75T01997 refers to Alumina products 16P01805 and 16C00507 while the proposed commercial Alumina cartridge is product number 40P02585. Explain how the products differ and why the results obtained with alumina cartridge 16C00507 are applicable to alumina cartridge 40P02585.

PRODUCT QUALITY CMC

1. You have indicated that,
   - the flow rate of (b) (4) was optimized to maximize the (b) (4) step.
   - the flow rate of the (b) (4) the ABEC column.
   - the flow rate of the (b) (4) was optimized to maximize product yield.

   You will need to describe:
   a. what are the optimized flow rates
   b. how the maintenance of optimized flow rate will be assured in the commercial generator
   c. if any monitoring or recording of such rates is available

2. You have indicated that for commercial use, the "K2 ^{99}MoO4 Solution in 5M KOH / (b) (4)).

   You will need to submit data for three commercial batches to NDA (or the DMF).

3. In the specifications for potassium molybdate Mo 99 solution, you control the (b) (4) and other impurities at (b) (4) You will need to describe how the (b) (4) impurities (b) (4) will be controlled.

4. During development the container(s) (bottle(s)) were filled with (b) (4)

5. The following information regarding the quality attributes for ABEC resin is needed:
   a. critical attributes for the performance of the resin (including, what was considered and why it is critical or not critical)

b. listing, based on the method of synthesis, of impurities that can be present and can leach into the product; safety of leachable impurities, if any
c. bed density of the resin in packed column

6. You have indicated that based on preliminary performance testing the ABEC resin has a (b) (4) year shelf life. However the performance testing data are not in the NDA. Additionally, you are performing a prospective, protocol driven stability study to define the stability characteristics of the ABEC resin contained within the Primary Separation Cartridge (b) (4)). These data are not available. You will need to provide the data in the NDA.

7. (b) (4)

8. We note that you intend to supply reagents and other auxiliary materials in kits (e.g., Reagent Kit, Cleaning Kit, Collection Kit). You will need to describe the components and composition of each kit, manufacturer of the kits, and controls for the kit to assure that each kit meets preset acceptance criteria. You also will need to have label for each kit. The expiration date on the kit should be established based on the shortest expiration date of the components in the kit.

9. It is not clear if there will be a change in the manufacturer and packaging (container closure system) of the reagent solutions used in the generator. Be advised that any change would require submission of complete chemistry, manufacturing and controls information (including the stability data) for that solution.

10. We note that the commercial TechneGen Generator will be manufactured by (b) (4) in (b) (4) We also note that (b) (4) has not manufactured the entire TechneGen generator. You will need to provide information and data that this company is capable of manufacturing the generator.

11. We note that the current version of the TechneGen Instrument software (used for making the NDA product) may not be the version used in commercial instruments. You will need to provide batch data for sodium pertechnetate Tc 99m injection product obtained using the commercial version of the TechneGen Instrument and software. Also, for such batches, the molybdate Mo 99 solution should be manufactured in the commercial facility.

12. The molybdate Mo 99m solution needs to be performance tested (at least on some predefined schedule) to confirm that it continues to produce sodium pertechnetate Tc

99m injection of intended quality. You will need to provide such testing protocol and schedule.

13. Your data on Ceretec radiolabeling indicates that there can be issues with the labeling of radio-pharmaceutical kits because of higher volumes or lower activity obtained from TechneGen generators at later time points. Clarify how this will be addressed in the labeling.

14. You have indicated that the drug product post-approval stability protocol will be performed on one lot annually using the largest Mo99 source size at a designated nuclear pharmacy or an authorized testing laboratory. In the protocol add a statement that these data will be collected and submitted to the NDA annual report. Provide an amended post-approval stability protocol.

15. The referenced DMF #26592 for the TechneGen Generator System is deficient. You will need to adequately resolve the deficiencies prior to approval of this NDA.

16. The proposed manufacturing facilities readiness to manufacture TechneGen and associated components is inadequate. All manufacturing facilities need to be adequate prior to approval of this NDA.

17. Your application referenced the Drug Master File (DMF) 26592. This DMF was found inadequate to support your submission and a deficiency letter was sent to the DMF holder on October 10, 2013. These deficiencies must be adequately addressed before this application can be approved. As part of your response to this letter, include the date the DMF holder amended their DMF to address the deficiencies.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, 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.

FACILITY INSPECTIONS

During a recent inspection of the (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. Additionally, field investigators could not complete inspections of the NorthStar Medical Radioisotopes, LLC and (b) (4) manufacturing facilities because the facilities were not ready for inspection. Satisfactory inspection is required before this application may be approved. Please notify us in writing when these facilities are ready for inspection.

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.

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.

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 Alberta Davis-Warren, Regulatory Project Manager, at (301) 796-3908.

Sincerely,

{See appended electronic signature page}

Libero Marzella, M.D., Ph.D.
Acting Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

LIBERO L MARZELLA
11/04/2013