CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202158Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	11/1/2013
From	Libero Marzella MD, PhD
Subject	Division Director Summary Review
NDA # **Supplement #**	202158 0
Applicant Name	NorthStar Medical Radioisotopes, LLC
Date of Submission	01/04/2013
PDUFA Goal Date	11/04/2013
Proprietary Name / **Established (USAN) Name**	TechneGen Generator System Sodium Pertechnetate Tc99m Injection
Dosage Forms / Strength	Sterile solution for intravenous injection or oral administration/ (b) (4)
Indications	Sodium Pertechnetate Tc99m Injection produced by a TechneGen Generator System is a diagnostic radiopharmaceutical for use in children and adults for: -Brain imaging including cerebral radionuclide angiography -Thyroid imaging -Salivary gland imaging -Placenta localization -Blood pool imaging including radionuclide angiography -Urinary bladder imaging to detect vesicoureteral reflux. In addition, it is indicated for use in adults for: -Nasolacrimal drainage imaging. In addition Sodium Pertechnetate Tc99m Injection is for use to reconstitute reagent kits (Technetium Tc99m Kits)
Action	Complete Response

Material Reviewed **OND Action Package, including**:	**Names of discipline reviewers**
Medical Officer Review	Phillip B Davis, MD
Pharmacology Toxicology Review	Siham Biade, PhD; Adebayo A Laniyonu, PhD
Chemistry Manufacturing Controls Review	Ravindra K Kasliwal, PhD
Microbiology Review	Jessica G Cole, PhD
Clinical Pharmacology Review	Christy S John, PhD
CDTL Review	Eldon Leutzinger, PhD
Pediatric and Maternal Health	Erica Radden, MD
CDER/OSE/DRISK	Robert G Pratt, PharmD
CDRH/OSEL/DSFM	Prasanna Hariharan, PhD
CDRH/OSEL/DESE	Joseph Jorgens III, PhD

OND = Office of New Drugs
OSE = Office of Surveillance and Epidemiology
DRISK = Division of Risk Management

CDTL= Cross-Discipline Team Leader
CDRH = Center for Devices and Radiological Health
CDER = Center for Drugs Evaluation and Research
OSEL = Office of Science and Engineering Laboratories
DSFM = Division of Solid and Fluid Mechanics
DESE = Division of Electrical and Software Engineering

1. Introduction

This 505(b)(2) new drug application (NDA) for the TechneGen Generator System for the preparation of Sodium Pertechnetate TC99m injection is submitted by NorthStar Medical Isotopes, LLC. The TechneGen generator is an automated radionuclide isolation and purification system to be used in a radiopharmacy for the preparation of the active pharmaceutical ingredient (API) sodium pertechnetate Tc99m from a solution of molybdenum-99 (^{99}Mo). The final radioactive drug product Sodium Pertechnetate Tc99m Injection is the same approved product prepared with the two technetium generators currently marketed in the US. The drug is designed to meet the purity and quality standards for Sodium Pertechnetate Tc99m Injection in the USP monograph.

This NDA submission contains no new clinical or preclinical data and none are needed because the final drug product ($NaO_4{}^{99}Tc$ injection) for this NDA is the same product prepared with the two technetium generators marketed in the US. The listed drug that this NDA relies on is the Ultra-TechneKow DTE generator (Covidien) approved in 1973. The second technetium generator Technelite (Lantheus) was approved in 1976. Technetium generators produce $^{99m}TcO_4^-$ (daughter isotope) from the nuclear decay of $^{99}MoO_4^{2-}$ (parent isotope). In the case of rubidium generators (CardioGen-82) the radionuclide rubidium-82 (^{82}Rb) is produced by the nuclear decay of Strontium 82 (^{82}Sr).

Sodium Pertechnetate Tc99m Injection has been in clinical use for many years to image perfusion and function in a variety of organs. The current high specific activity, concentrated product is primarily used in a modern nuclear pharmacy primarily for radiolabeling various diagnostic imaging drugs that are marketed as nonradioactive drug kits. The radiolabeled imaging drugs are used for single photon emission computed tomography (SPECT) imaging. From a regulatory perspective the radioactive drug under review in this NDA includes the radionuclide and the radionuclide generator used to prepare this substance as required by 21CFR 310.3(n).

The Technegen generator system consists of an instrument which houses two isolation and purification cartridges, reagent reservoirs, fluid lines, valves, pumps, control electronics and shielding; a container system for the source solution of molybdenum-99; a computer system with a user-interface that controls the instrument operations. The user is required to aseptically assemble and install into the instrument the sterile reagent solutions, separation cartridges, Tc99m collection vial assembly and the molybdenum-99 source solution vessel. After completing the installation, the user starts the automatic elution process and runs it under computer control. The Technegen system's sterile components are replaced after a specified number of elutions. The fluid paths (lines, valves) are sanitized, rinsed and (b) (4) once weekly.

Drs. Leutzinger and Kasliwal point out that the manufacture of the $^{99}MoO_4^{2-}$ proposed for use with the TechneGen generator and consequently the design of the generator differ greatly from the $^{99}MoO_4^{2-}$ manufacture and design of the approved generators Ultra-TechneKow (Covidien) and Technelite (Lantheus). The approved generators require high specific activity $^{99}MoO_4^{2-}$ produced by the fission of enriched uranium targets subjected to neutron bombardment in nuclear reactors. The approved technetium generators are manufactured using a single, compact alumina (Al_2O_3) column to which $^{99}MoO4^{2-}$ is adsorbed. A simple one-step elution with a small volume of saline is required to separate the daughter $^{99m}TcO_4$ from the parent $^{99}MoO4^{2-}$.

On the other hand the TechneGen Generator System is designed for use with low specific activity $^{99}MoO_4^{2-}$ obtained from the neutron bombardment of ^{98}Mo (n, γ). The TechneGen generator contains two chromatography columns (one resin (ABEC), the other alumina). Contrary to the operation of the marketed generators $99MoO42^-$ is not bound by the resin column. For this reason the 99mTcO4- can be isolated while the $^{99}MoO_4^{2-}$ is recovered and regenerates a $^{99}MoO_4^{2-}/^{99m}TcO_4^-$ mixture. $^{99m}TcO_4^-$ is eluted from the resin column, in reverse flow, and pumped to the alumina column, where it passes through and is finally collected in a receiving vessel.

The following are the key steps involved in the use of the generator. (b) (4)

The FDA CMC reviewers have concluded that the API production process and process controls are reasonably robust and final product specifications are acceptable. I concur with their assessment. A number of CMC deficiencies remain to be addressed and will be detailed below.

The microbiology reviewer Jessica Cole, Ph.D. points out that the approved technetium generators are closed sterile systems that are aseptically eluted with few simple manipulations and are in use for two weeks. On the other hand, the TechneGen generator is a more complex non-sterile system that uses sterile reagent solutions and some sterile components and requires that the user assemble multiple parts aseptically. The studies to demonstrate the microbiological control of this complex manipulation –intensive system were seriously deficient in design and conduct. I concur with Dr. Cole's assessment that this is a critical deficiency.

I concur with the assessment by the FDA reviewers that the NDA lacks adequate labeling for the safe use of the generator. Drs. Leutzinger, Cohen and Davis point out that adequate

procedures and manuals for training and for operations of the generator have not been fully developed and tested.

2. Background

Clinical Importance of $^{99m}TcO4^-$

I concur with the assessment by the NDA reviewers that the sustained uninterrupted availability of $^{99m}TcO4^-$ is of great importance to nuclear medical practice. $^{99m}TcO_4^-$ is the most commonly used diagnostic radiopharmaceutical used in nuclear medicine. It accounts for approximately 85% of the diagnostic procedures in the U.S. $^{99m}TcO_4^-$ has a half-life of approximately six hours and emits low energy photons that can be imaged using a gamma camera in single photon emission tomography. The short half-life of the radionuclide is suitable for the preparation and administration of the final product followed by imaging while minimizing the exposure of the patients to radioactivity. $^{99m}TcO_4^-$ can be chemically incorporated in several tracers (marketed as non radioactive drug kits) that are indicated for evaluating perfusion and function of various body organs. Drug shortages have occurred because of planned and unplanned shut-downs of aging nuclear reactors required for the manufacture of ^{99}Mo.

Public Health Importance of New Technology for Mo99 Production

I concur with the assessment by the chemistry and clinical reviewers that the TechneGen generator system while technically more challenging for the user represents a potential important advance to the public health because it could contribute to the maintenance of a stable supply of $^{99m}TcO_4^-$ from non-fission produced ^{99}Mo.

A shift in the manufacture of ^{99} Mo from highly enriched uranium to low enriched uranium is under way as mandated by Congress. Alternatives to fission-produced ^{99}Mo are also being sought globally to further diminish risks from fission waste and security concerns related to nuclear proliferation. DMIP and ONDQA believe that the development of new production methods for ^{99}Mo that are non-fission and also non-reactor based is a highly desirable public health objective. This objective poses substantial scientific, technical and commercial challenges and various government agencies in the US are actively encouraging and supporting these activities.

Drs. Leutzinger, Kasliwal, Duffy, Cole, and other FDA staff from CDER and CDRH have provided frequent guidance to the manufacturer during the development of this innovative product. These intensive discussions and requests for advice and information have continued during the NDA review and have posed challenges for the review team. Drs. Kasliwal, Leutzinger, and Cole have outlined a plan that the manufacturer needs to follow to address the shortcomings of the current NDA submission. I agree with their analysis and recommendations.

3. CMC/Device

CMC

I concur with the conclusions reached by the chemistry reviewer Dr. Ravindra Kasliwal regarding the lack of sufficient data on the manufacturing of the drug product and drug substance. These issues preclude approval of the product.

The reviewer determined that the NDA needs data on the following.

- Optimization of flow rates for (b) (4) (b) (4). If the flow rates are not optimal, $^{99}MoO_4^{2-}$ breakthrough into the pertechnetate product may result, and affect the concentration of pertechnetate in the saline eluate.

- Three commercial batches of $K_2{}^{99}MoO_4$

- Resin (ABEC) column quality. Specifications of critical attributes for column performance (e.g. particle size and its distribution, how well the column is packed) are needed. The organic-based resin has the potential to introduce impurities in the final product.

- Specifications for $K_2{}^{99}MoO_4$. Specifications need to be established for the potential radionuclidic impurities from the other naturally occurring Mo isotopes and from other metal impurities in the naturally-occurring Mo that might be produced during the neutron bombardment.

- TechneGen Generator Performance. The ability of (b) (4) to manufacture the generator has not been demonstrated, and the software that will be used in the computer control has not been finalized.

Lesser issues involving Reagents, Reagent Kits and other Equipment need to be addressed.

Microbiology Product Quality Issues

I concur with the conclusions reached by the clinical microbiology reviewer that there are critical outstanding clinical microbiology sterility issues that preclude product approval.

The microbiology reviewer Jessica Cole, Ph.D. recommends a complete response based on an assessment of a high risk for producing a product that is not sterile. The TechneGen system, poses greater risks than the approved technetium generators. The TechneGen generator is a non-sterile system that uses sterile reagent solutions and some sterile components and requires that the user assemble multiple parts aseptically. In addition to the generator, the container system for the source solution of $^{99}MoO_4^{2-}$ / $^{99m}TcO_4^-$ and the computer four sterile disposable kits are needed to elute the system.

(b) (4)

The studies to demonstrate the microbiological control of the TechneGen system generator were seriously deficient in design and conduct. For example Dr. Cole pointed out that for certain cleaning protocol validation studies, samples to evaluate bioburden of the system were collected after sterile filtration and sampling was performed only immediately after running a cleaning protocol and inadequate positive controls were used. In addition the submission lacked adequate human factor studies and training to verify the safe use of the generator.

Dr. Cole considers TechneGen to be a mobile aseptic processing facility requiring extensive validation studies, training programs, and routine onsite inspections by FDA. Dr Cole is concerned that if approved, this NDA could create a regulatory precedent for the use of a radionuclide generator outside the aseptic manufacturing paradigm. The reviewer recommended discussion of the microbiology issues at a regulatory briefing before taking a regulatory action. DMIP in consultation with ODE IV decided to focus on completing the review of the present submission and deferred a decision on a Center-wide briefing until the applicant provides data to address the question of whether or not the cleaning process can consistently remove bioburden present in the system.

The microbiology deficiencies to be communicated to the applicant include the following: the transfer fluid lines pose a risk for microbial contamination and are a potential source of bioburden and endotoxin; the cleaning protocol is not adequate to remove bioburden from the system; the sterilizing filters are essential for patient safety, and need to be tested for integrity after use; media fill studies need to be performed by the end user at the final installation site. Other microbiology deficiencies include lack of process validation, validation of the (b) (4) sterilization, peroxide (3%) cleaning validation studies, and lack of tests for whether the final dosage form meets the proposed specifications.

Dr Cole has identified critical deficiencies that preclude an assessment of the microbiological quality of the product as prepared in actual use. If the control of the process cannot be demonstrated it is possible that design changes might be required to develop a more robust generator system.

Device:
The reviewer from the Division of Solid and Fluid Mechanics (Dr. Prasanna Hariharan) identified the following unresolved issues with the fluid path in the TechneGen generator.

- Optimization of pressure and need for flow monitoring and sensor controls including potential for system shut down or alerting the operator if there is a problem with fluid flow
- Need for shielding of fluid lines and potential for kinking
- Malfunctioning of valves and potential for incomplete cleaning

The reviewer from the Division of Electrical and Software Engineering (Dr. Joseph Jorgens) classified the level of concern posed by the software as moderate. The reviewer determined that inadequate information has been provided to permit a substantive review of the software safety. A listing of needed information include description of clinical hazards and methods of controls developed and tested, software design, programming language and specifications, unresolved defects, tools used to detect run time errors.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewers Dr. Biade and Laniyonu that there are no nonclinical issues for this NDA. Sodium Pertechnetate Tc99m is an FDA-approved product. No nonclinical information was submitted and none were needed.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer Dr. Christy John that there are no outstanding clinical pharmacology issues that preclude approval. No clinical pharmacology or clinical studies were conducted for this NDA. The proposed package insert uses the same language as the package inserts for Ultra-TechneKow and Technelite.

6. Clinical Microbiology

This section is not applicable to this application. No clinical microbiology data were included in the submission.

7. Clinical/Statistical-Efficacy

I concur with the assessments of the clinical reviewer Dr. Phillip Davis. In the primary review filed 5/27/2013, the clinical reviewer provided recommendations regarding the indications and dosing and administrations sections of the proposed drug label. Among others, these recommendations included deleting" Placenta Localization, editing the "Brain Imaging" and "Blood Pool Imaging" indications, and the 'Dosage" section of the label. These labeling comments will not be communicated to the applicant at this time.

8. Safety

User and Training Manuals and Human Factors Study

I concur with the assessment of the clinical reviewer Dr. Davis that the NDA lacks sufficient information to fully evaluate the safe use of this Tc-99m generator.

In the 3/18/2013 Filing Issues Identified document, FDA noted that the sponsor had not sufficiently developed plans for implementation and use of the Technegen system at clinical facilities. The reviewers determined both the operations manual and human factors engineering/usability report needed substantial revision in order to complete a review of the NDA. The reviewers recommend that the applicant develop a systematic process for training end users and perform a human factors assessment study to determine the sufficiency of the applicant's user manual and training program, once fully developed.

At a teleconference on 7/17/2013 the FDA discussed a revised user manual and human factors validation protocol. FDA recommended the document be revised into more of a "how to" document that concisely outlines the process for using the system, and contains information on corrective actions for generator malfunction or user error. The Agency also recommended that the applicant develop an analysis of critical hazards that could result from incorrect use of TechneGen and identify the worst case scenarios for both the user and the patient, and the corresponding step of TechneGen use where an error could occur.

I concur with the recommendations of the Social Sciences reviewer Dr. Barbara Cohen regarding the human factors validation protocol. The reviewer recommended the following:

- Evaluation of critical tasks for the user to accomplish correctly and discussion of whether failure to accomplish each task would constitute a safety issue, an efficacy issue, or both.
- A label comprehension study to test the user manual first with a representative sample of potential users in order to optimize comprehension prior to using the manual in a human factors test.
- Stand-alone testing of the user's manual in a group of trained users.
- Testing under conditions of time pressure, continued interruptions and/or poor lighting.
- Inclusion of metrics that are objective, and quantifiable.
- Estimate of sample size that incorporates the factors studied.

9. Advisory Committee Meeting

No advisory committee meeting was needed.

10. Pediatrics

The applicant proposes the same indications and dosing requirements as the reference listed drug. The application does not provide for a new indication, dosage form, dosage regimen or route of administration. For these reasons the Pediatric and Maternal Health Staff (Erica Radden MD) determined that the application does not trigger the Pediatric Research and Equity Act (PREA).

11. Other Relevant Regulatory Issues

Manufacturing Sites
The FDA field investigators have not been able to verify the readiness of the proposed facilities to manufacture TechneGen and associated components.

The investigators have identified important deficiencies with a manufacturing facility (b) (4) that formulates, fills, sterilizes, packages, and labels reagent Solutions used in the elution of TechneGen. Additionally, field investigators could not complete inspections of the NorthStar Medical Radioisotopes, LLC and (b) (4) Inc. manufacturing facilities because the facilities were not ready for inspection. (b) (4) is particularly important because they are designated as the manufacturer for the entire generator.

Risk Management
The reviewer from The Division of Risk Management (Dr. Pratt) agreed that the operation of the TechneGen system is complex and involves many more steps for the user compared with production of ^{99m}Tc using conventional generators. The applicant has proposed a training program for users that may include lectures, review of the user manuals, hands on demonstration, and assessment of participant performance on the operational tasks. Individuals successfully completing the training would receive certification of completion. The details of the training program have not been submitted to the NDA.

Because of the deficiencies related to verification of system design and performance, microbiological control, and the need for substantial revision to the operator manuals and human factors study, DRISK is unable to determine if a REMS is necessary for the TechneGen system. DRISK will continue to follow this NDA and if new safety information or analyses become available, the decision can be reevaluated.

12. Labeling

Labeling reviews by all the disciplines was deferred pending resolution of the issues identified during this review cycle.

13. Decision/Action/Risk Benefit Assessment

I concur with the recommendation made by the FDA primary and secondary reviewers in chemistry, microbiology, and clinical disciplines that several serious deficiencies in this application need to be addressed by the applicant.

The most critical NDA deficiency is the lack of sufficient data to determine if the TechneGen system can provide the required sterility assurance level for the product. The NDA data do not support the claim that (b) (4) .
Robust microbiological validation studies will be required to verify the microbiologic quality of this aseptically prepared product. A validated training program for the users and requirements for user qualification will also be necessary. Ongoing oversight by the manufacturer of the safe use of the system may be necessary. At present there is no consensus among reviewers within and across disciplines on whether or not these objectives can be achieved with the product as currently designed and/or the current process controls. In particular, the microbiology reviewers regard the TechneGen generator system as a mobile aseptic manufacturing process requiring different controls and regulatory oversight than the marketed technetium generators which are designed for simpler aseptic elutions. The microbiology reviewers have provided specific advice to the applicant on how to develop the data necessary to address these issues.

The other important NDA deficiencies have been identified by the CMC reviewers. The most important of these deficiencies is the lack of adequate control of (b) (4) and product batch data are necessary. It is anticipated that these deficiencies will be readily addressed by the applicant. I concur with the basic CMC assessment that the manufacturing process is robust and that the drug product quality with respect to Tc99m yield, and level of contaminants from the drug substance and the columns (e.g. Mo99m, aluminum) is acceptable.

Finally the lack of optimal user and training manuals and of validation studies for the manuals is an important deficiency highlighted by the clinical reviewer. The applicant is developing the final versions of the manuals and the verification protocols with an experienced consultant and it is anticipated that they will address these deficiencies.

Tc99m is a medical imaging drug in wide use in the US for diagnostic nuclear medicine procedures. The development of reliable sources of this drug that do not depend on the use of enriched uranium is an important public health objective. The rationale is to minimize environmental risks and risks from intentional diversion and misuse of enriched uranium. The chemistry and manufacturing process under development by the applicant could represent and important advancement.

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/s/

LIBERO L MARZELLA
11/04/2013