

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202158Orig1s000

PRODUCT QUALITY REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: 29-Jan-2018

From: Ravindra K. Kasliwal, Ph.D.
CMC Reviewer
Branch VI, DNDC-II
ONDP / OPQ

Through: Danae Christodoulou, Ph.D.
Branch Chief
Branch VI, DNDC-II
ONDP / OPQ

Re: NDA 202158, RadioGenix™ System
NorthStar Medical Radioisotopes, Inc.
1800 Gateway Blvd.
Beloit, WI 53511

Subject: Request for a Waiver of Bioavailability Studies.

In accordance with 21CFR Part 320.22(b)(1), NorthStar Medical Radioisotopes, LLC has requested that in vivo BA/BE studies be waived as the Sodium Pertechnetate Tc 99m Injection product obtained from RadioGenix System (technetium Tc 99m generator) is a parenteral solution with the primary route of administration by intravenous injection and that the drug product contains the same active and inactive ingredients in the same concentration in the patient dose as the reference listed drug products (Technelite® (NDA 017771) and UltraTechneKow® (NDA 017243)).

Both the Technelite® (NDA 017771) and UltraTechneKow® (NDA 017243) technetium Tc 99m generators produce injection solution of sodium pertechnetate Tc 99m in 0.9% sodium chloride injection with a pH of 4.5 -7.5. While the amount of sodium pertechnetate Tc 99m produced depends on the generator size (i.e., amount of Molybdenum 99), the patient dose is measured in terms of mCi amount is the same.

The proposed RadioGenix™ System (technetium Tc 99m Generator) produces sodium pertechnetate TC 99m injection from a 6 Curie source of Molybdenum Mo 99. While the source (method of production) of Mo 99 is different, it does not impact the final sodium pertechnetate TC 99m injection product. The final product contains sodium pertechnetate Tc 99m in 0.9% sodium chloride with a pH of 4.5 -7.5. Thus, RadioGenix™ System produced product has the same Sodium pertechnetate Tc 99m active ingredient and same 0.9% sodium chloride solution inactive ingredient as the reference listed drug.

The dose of sodium pertechnetate Tc 99m injection is administered to human subjects based on mCi amounts. Since the radioactivity continuously decays, the volume of solution can differ for the same mCi amount. This is also the case for different generators sizes, the larger generators provide greater sodium pertechnetate Tc 99m concentration than the smaller size generators. The difference in pertechnetate concentration are, however, inconsequential. For example, based on the specific activity of 3.4×10^6 Ci/gm (for carrier free pertechnetate Tc 99m) a 20 mCi amount of will contain 68 μ g of pertechnetate. This is an extremely low mass amount in 9mg/mL sodium chloride solution. These low amounts are not expected to have any significant effect on the physical property (e.g., viscosity or tonicity) of the solution

Based on above observations and the fact that the primary route of administration is intravenous, the bioavailability of this RadioGenix™ System produced sodium pertechnetate Tc 99m injection product is self-evident. Therefore, FDA deemed adequate information is provided to support the waiver request for conducting any relative bioavailability (BA) or bioequivalence (BE) study for RadioGenix™ System.



Ravindra
Kasliwal

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Danae
Christodoulou

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QUALITY ASSESSMENT



OPQ Integrated Quality Assessment final NDA 202158 Resubmission Review Date: 1/24/2018

Drug Product	RadioGenix™ System (Technetium Tc 99m Generator) For production of technetium Tc 99m injection, USP
Strength	Variable; generator size, 6 Ci
Route of Administration	IV injection
Rx/OTC Dispensed	Rx
Applicant	Northstar Medical Radioisotopes, LLC, 1800 Gateway Blvd., Beloit, WI 53511
US agent, if applicable	N/A

Quality Review Data Sheet

- LEGAL BASIS FOR SUBMISSION: 505b2
- RELATED/SUPPORTING DOCUMENTS:
 - DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETE	REVIEWER
26592	II	NorthStar Medical Isotopes	TechneGen Generator System			Ravi Kasliwal Robert Meyer

- DMF's 26426, (b) (4) are found adequate (see NDA review, Ravi Kasliwal, Ph.D., 10/07/2013)

A. Other Documents: N/A

- CONSULTS: N/A

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Ravindra Kasliwal, Ph.D.	ONDP/DNDAPI
Drug Product	Ravindra Kasliwal, Ph.D.	ONDP/Branch VI/Division II
Microbiology	Jessica Chiaruttini, Ph.D.	OPQ/OPF/Microbiology
Facility Device	Krishnakali Ghosh, Ph.D. Robert Meyer, B.S., M.E.	OPQ/OPF/DIA/B1 CDRH/ODE
Project/Manager (R.Ph)	Thao Vu	OMPT/CDER/OPQ/OPRO/ORDP MI/RBPMBI
Application Technical Lead	Eldon E. Leutzinger, Ph.D.	ONDP/Branch VII/Division II
<u>Environmental Assessment (EA)</u>	Ravindra Kasliwal, Ph.D.	ONDP/Branch VII/Division II

Table 2 Documents			
DOCUMENT	RECEIPT DATE	DESCRIPTION	Section/reviewer
Resubmission	5/8/2017	Class 2 response to action letter of 11/4/2013	CMC product quality/Ravindra Kasliwal, Ph.D.

Executive Summary

I. Recommendations

APPROVAL, based on the risk evaluations and recommendation of CMC Product Quality, Microbiology Product Quality, with a Post-Marketing Commitments (PMC), and Manufacturing Facility Inspections and CDRH (including a PMC by CDRH).

A. Recommendation and Conclusion on Approvability

N/A

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Quality Assessments

BACKGROUND:

The **RadioGenix System** is a new version of the technetium generator ($^{99}\text{Mo} / ^{99\text{m}}\text{Tc}$), intended to be used in a nuclear pharmacy to produce Sodium Pertechnetate Tc 99m Injection USP. Installation at nuclear pharmacies will be by NorthStar Medical Radioisotopes, who will also perform IQ and OQ. The System is designed to be used with low specific activity ^{99}Mo derived from non-fission processes, e.g., $^{98}\text{Mo}(n,\gamma)^{99}\text{Mo}$. As a radionuclide generator, RadioGenix System is classified as a drug (21 CFR 310.3(n)).

A Complete Response Letter was communicated to Northstar Medical Radioisotopes, LLC on November 4, 2013 detailing the deficiencies from Clinical, Product Quality CMC, CDRH, Product Quality Microbiology, as well as labeling (package insert instructions for preparation and safe use of the generator system, user manual). There were recommendations (teleconference, 7/17/2013) from the clinical discipline detailing how to revise the user and training materials, and how to design and conduct a human factors study for the acquisition of meaningful data in support of safe use of the generator system. Additionally, there were multiple deficiencies in DMF 26592 regards the device system (CDRH), and were handled under separate cover. The Resubmission (May 8, 2017) is in response to address the deficiencies in the Complete Response Letter.

WORKING PRINCIPLE OF THE RADIOGENIX SYSTEM:

Use of low specific activity ^{99}Mo with the RadioGenix System is made possible by use of an ABEC column (Aqueous Biphasic Extraction Chromatography), connected in series

with an Alumina column (aluminum oxide). Together with ancillary equipment consisting of tubing lines and valves, the System is housed in a computer-controlled synthesis module. The ABEC column is filled with monoethylated polyethylene glycol (PEG), chemically bonded to styrene-divinylbenzene resin beads. $^{99}\text{MoO}_4^{2-}$ in 5M KOH (alkaline pH) is loaded onto the ABEC column. (b) (4)

, so that $^{99\text{m}}\text{TcO}_4^-$ is retained on the ABEC column, while $^{99}\text{MoO}_4^{2-}$ passes through and is recovered. The ABEC column is subsequently rinsed with 5M KOH, whereupon the removal of all $^{99}\text{MoO}_4^{2-}$ is completed. Following loading and washing (5M KOH, followed by 1.5M sodium acetate), $^{99\text{m}}\text{TcO}_4^-$ is removed from the ABEC column with saline. This is done in reverse-flow. The eluate from ABEC is routed to an Alumina column. Any $^{99}\text{MoO}_4^{2-}$ left in the eluate from ABEC is retained on Alumina. Elution of the Alumina column (in reverse-flow) with saline affords the Sodium Pertechnetate Tc 99m Injection USP ($\text{Na}^{99\text{m}}\text{TcO}_4$).

Although the function of ABEC to separate $^{99\text{m}}\text{TcO}_4^-$ from $^{99}\text{MoO}_4^{2-}$ is the same as it is on Alumina in the conventional technetium generator, it does it by retention of $^{99\text{m}}\text{TcO}_4^-$, and release of $^{99}\text{MoO}_4^{2-}$ into the stream that is recovered, opposite to how it is done with Alumina only. **Addition of ABEC separation technology is the distinguishing feature that makes RadioGenix System unique in the panel of approved technetium generators**, the novelty of which creates a potential solution to the problem of the absence of a U.S. source of ^{99}Mo , along with a potential means of satisfying the impending switch from HEU to LEU in the production of ^{99}Mo .

How ABEC Works -

Although the mechanism of metal ion partitioning in ABEC is poorly understood, it is a proven technology, having its roots in a type of LC, based on aqueous biphasic principles for which there is a significant body of experimental work. According to current theory, there is a thermodynamic basis for metal ion partitioning in ABS (aqueous biphasic systems). At high ionic strength, ions (such as TcO_4^-), having a relatively small negative Gibb's free energy of hydration (ΔG_{hyd}), tend to partition to the PEG-rich phase in ABS – “salt out,” whereas those (such as for MoO_4^{2-}) that have large negative free energy of hydration move into the aqueous-phase. Since both biphasic systems are PEG-based, similar behavior occurs with ABEC, so that TcO_4^- is retained in the polystyrene-bonded PEG, while MoO_4^{2-} is excluded, the latter passing into the aqueous phase. At low ionic strength, the distribution changes, and TcO_4^- is no longer retained in the polystyrene-bonded PEG phase in ABEC [*G. Huddleston, et.al., in Metals in Biotechnology, Vol.11, Humana Press, Inc., Tolowa, N.J.*].

SUMMARY OF PRODUCT QUALITY ISSUES:

A. Drug Substance [USAN Name] Quality Summary

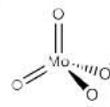
Sodium Pertechnetate Tc 99m, $\text{Na}^{99\text{m}}\text{TcO}_4$ (produced by RadioGenix System)

Identity:

Product Quality always begins with an understanding of what is the identity of the drug substance, in this case $\text{Na}^{99\text{m}}\text{TcO}_4$, for which the greatest application is in the radiolabeling of technetium radiopharmaceutical kits. In this paradigm, the **linchpin of**

all chemical quality attributes (CQA) is Identity. Here, the chemical entity is that in the bracket, along with its counterion (Na^+) in the geometric structure,

$\text{Na}^+ \left[\begin{array}{c} \text{O} \\ \parallel \\ \text{O} - \text{Tc} - \text{O}^- \\ \parallel \\ \text{O} \end{array} \right]$, where $\text{Tc} = {}^{99\text{m}}\text{Tc}$ ($t_{1/2}$ 6 hrs, and γ radiation of 140.5 KeV). It is generated on decay of ${}^{99}\text{Mo}$ in the oxyanion of molybdate,



which is approximately preserved in the pertechnetate structure $[{}^{99}\text{Mo}(\text{VI})\text{O}_4^{2-} \rightarrow {}^{99\text{m}}\text{Tc}(\text{VII})\text{O}_4^- + \beta^- + \bar{\nu}(\text{antineutrino})]$. The half-life of ${}^{99}\text{Mo}$ is 66 hrs. The tetrahedral structure for molybdate (${}^{\text{Nat}}\text{MoO}_4^{2-}$) is well-accepted, having its origin of structure proof dating back to the mid 1960's [*R. H. Busey and O.L. Keller, Jr., Journal of Chemical Physics 41, 215 (1964)*], through Raman crystal spectra. These investigators also showed by correlation of Raman aqueous spectra of molybdate and pertechnetate (${}^{99}\text{TcO}_4^-$) that the structure of the latter oxyanion was tetrahedral.

The change from ${}^{99}\text{Mo}$ to ${}^{99\text{m}}\text{Tc}$, all within the oxyanion molecular framework, does not just passively happen (like in most chemical reactions, except for high energy systems). **At the point of change, there is a “recoil” by the daughter nucleus (${}^{99\text{m}}\text{Tc}$), the recoil energy of which depends on the energy of the β^- and $\bar{\nu}$ (antineutrino), and their emission directions. It is known that recoil energies exceed most bond energies.** Since the ${}^{99\text{m}}\text{Tc}$ nucleus is attached in the oxyanion framework of the parent system, it is interesting (if not behooving) that a molecular change is not induced into the oxyanion structure during recoil, given the larger mass of Tc. In this instance, retention of the oxyanion structure in the product (as was initially present in the parent system) is apparently maintained, including the tetrahedral geometry. That this is so for ${}^{99}\text{Mo}/{}^{99\text{m}}\text{Tc}$, however, is fortunate. For if it were not, that would likely change the entire landscape of the radiochemistry of the technetium generator (${}^{99}\text{MoO}_4^{2-} \rightarrow {}^{99\text{m}}\text{TcO}_4^- + \beta^- + \bar{\nu}$), and all of the subsequent chemistry during radiolabeling of the technetium radiopharmaceuticals. Further discussion of this curiosity is beyond the scope of this document, but is mentioned here, because it is a testimony to the robustness of the technetium generator, seemingly appropriate with the timing of the RadioGenix System, as it represents the first major advance in the long saga of the technetium generator.

In its earliest form, the technetium generator was invented at the Brookhaven National Laboratories in 1957. It became available in 1960 from BNL, but did not become commercially available until 1964. As UltraTechnekow (Curium/Covidian/Mallinckrodt), it was approved by the FDA in 1973, and then again in 1976 as Technelite (Lantheus).

CMC:

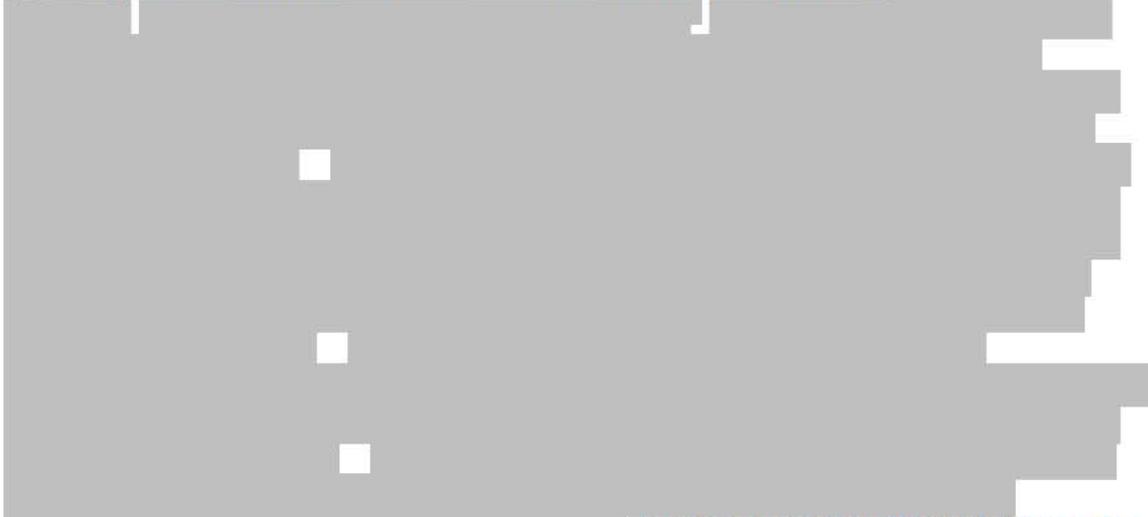
Some deficiencies remained from the first cycle -regards the $\text{K}_2{}^{99}\text{MoO}_4$ Solution in 5M KOH (b) (4)

[Redacted]

All these issues are

resolved with updates in the resubmission. But, the fundamental aspects of manufacture of this KOH solution remain the same as described in the MURR DMF 26426, which was found to be adequate. CONCLUSION: [Resolved](#)

(2) The specifications of the $K_2^{99}MoO_4$ solution includes controls for (b) (4)



[a more complete discussion is in the CDTL review, E. Leutzinger, Ph.D., DARRTS, 10/11/2013].

Because this nuclear process is not fission-based, it is not expected that the fission products as found in the ^{99}Mo used in the conventional technetium generator will be present in the ^{99}Mo used in RadioGenix System. Hence, it is not expected to find ^{89}Sr , or ^{90}Sr in this ^{99}Mo (nor, of course, those already mentioned in the previous paragraph). True with theory, ^{89}Sr and ^{90}Sr are not found in this ^{99}Mo . The most prominent of the radionuclidic impurities found in this ^{99}Mo are the following. (b) (4)



There is also a removal of many of these radionuclidic impurities when ^{99}Mo is separated from ^{99m}Tc by ABEC.

CONCLUSION: [Resolved \(DMF 26426\)](#).

Thirdly (3), generator sizes ($K_2^{99}MoO_4$ loads) from (b) (4) are proposed. However, information from development indicated that only (b) (4) Ci of $K_2^{99}MoO_4$ (filled into containers) was described. CONCLUSION: [Resolved \(through provision of additional information\)](#).

B. Drug Product [Established Name] Quality Summary
RadioGenix™ System (Technetium Tc 99m Generator) for production of technetium Tc 99m injection, USP. Generator size is 6 Ci

CMC:

In addition to the deficiencies for $K_2^{99}MoO_4$ identified in the CMC review (Ravi Kasliwal, Ph.D.) and communicated in the Complete Response Letter, there were multiple deficiencies ranging from the absence of optimized flow rates and their

maintenance in the commercial generator, to the absence of critical quality attributes of ABEC (including leachables and stability), absence of information on associated kits (Reagent Kit, Cleaning Kit, Collection Kit), performance testing of the $K_2^{99}MoO_4$ and testing of the generator eluate in Ceretec to generator manufacturing. Numerous deficiencies were found in the labeling.

Optimized Flow Rates -

The pivotal component of the RadioGenix System is the ABEC column, since it extracts $^{99m}TcO_4^-$ from the $^{99}MoO_4^{2-}$ source and concentrates it on the column.

Although the exact mechanism of metal ion partition on ABEC is not fully understood (lit), chromatography theory of separation by partition processes dictates that there is an equilibrium involving mass transfer of solutes between mobile and stationary phases.

Too fast a flow rate may override this equilibrium, shifting its position enough toward the mobile phase to alter the distribution ratio and potentially the capability of the ABEC mechanism to establish efficient selectivity between $^{99}MoO_4^{2-}$ and $^{99m}TcO_4^-$, putting the latter at risk of not being fully extracted from the source.

There are two other accompanying critical corollaries. One (1) is that the $^{99m}TcO_4^-$ needs to remain sequestered on ABEC during the rinsing step ((b) (4) ; 1.5M sodium acetate) to enable efficient extraction. Secondly (2), the $^{99m}TcO_4^-$ needs to come off ABEC in as small volume of saline as possible so that it can be fed onto the Alumina column to assure final strengths (mCi/mL) of $^{99m}TcO_4^-$ similar to those from the conventional technetium generator. CONCLUSION: **Resolved**.

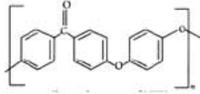
ABEC Media (for ABEC column) -

The foregoing on flow rates is a play on performance of the ABEC column in terms of the importance of flow rates in determining the distribution of $^{99m}TcO_4^-$ and $^{99}MoO_4^{2-}$ between stationary and mobile phases. How well an optimal distribution (**likened to a Critical Quality Attribute**) is achieved in each batch of ABEC for generator manufacture will be influenced by the condition of the ABEC media, relating to its chemical attributes, stability (and expiration date), and physical characteristics of ABEC (particle size) and media-pack in the column (bed density). Returning to “How ABEC Works” (page 3), it is important to understand how critical is the chemical and physical properties of ABEC. (b) (4)

(b) (4)

Leachables -

The chemical purity of the resultant pertechnetate product from the generator is governed by several factors. One of the most important of these factors is the **Leachables, a CQA** controllable with proper choice of material used in the manufacture of those components (tubing, valves, etc.) that come into contact with the fluid system. The leachables can be organic or inorganic. In RadioGenix System, these parts are made of PEEK (polyether etherketone), the chemical structure of which is the following:



It has a history of great stability against chemical and radiological insult. It also has reputed excellent stability to ozone, which in this instance is compatible with the procedures for sterilization of the internal portions of the generator system. Hence, there is no expected problem presented for leachables with PEEK in the fluid system of the generator. Nevertheless, NorthStar initiated a study for leachables, in accordance to USP <87> and USP <660>, subjecting to ozonated water, KOH, (b) (4) γ radiation. (b) (4) (b) (4) was performed at Argonne National Labs with a Van De Graaff Generator. Gamma radiation was performed at (b) (4) Ozonated water and KOH studies were performed at NorthStar Madison, WI. The results of these studies demonstrated that the PEEK and other materials within the internal system was resistant to the reagents and radiation (consistent with the history of the properties of PEEK). CONCLUSION: Resolved.

Reagents –

Product quality and stability of reagent solutions (associated Critical Quality Attributes) are important for maintenance of their capability to carry out their functional roles in the operation of radionuclide generators. There was absence of stability data for the (b) (4) reagent solution (ABEC (b) (4)

(b) (4)

CONCLUSION: Resolved.

In addition to the criticality of the ABEC (b) (4) solution (alkaline), there are the associated “Kits” in support of the operation of the generator, **Reagent Kits** (b) (4) reagent solutions of 3% H₂O₂, 5M KOH, 1.5M Sodium Acetate), **Primary Separation Cartridge wit ABEC resin**, the **Tc99m Product Kit w/TPC**. “TPC” consists of a column containing (b) (4), along with a (b) (4) μ m filter, and a vented (b) (4) Spike (for (b) (4) of the column eluate into a sterile 20 mL product vial). These kits were not well-defined in the original NDA, nor was there sufficient information provided on the reagents and other auxiliary materials used in the manufacture of these kits, along with defined specifications. There is also a **Sterilization Kit**, for which there was a paucity of information in its support. In their response (resubmission), a new Reagent Kit, Sterilization Kit and Tc99m Product Kit was developed and described in the RadioGenix Operator Guide.

It was also learned that they decided on adding [REDACTED] ^{(b) (4)} as a supplier for the reagent bags. That creates additional CMC and microbiology issues (as well as those regards the CGMP status of the manufacturing facilities). An amendment was submitted on this addition. The amendment was made a major amendment, and a letter was issued to Northstar that the user fee goal date was extended to February 8, 2018. CONCLUSION: **Resolved (with full descriptions of the kits and their components, specifications, etc.).**

Performance Testing -

One issue arose - the absence of performance testing of the $K_2^{99}MoO_4$ solution to confirm that it continues to produce Sodium Pertechnetate Tc 99m Injection meeting the established specifications; needed was the testing protocol and testing schedule. As radionuclide generators age (toward expiry), radioactivity of the eluates become less. Attendant with lesser radioactivity levels come larger volumes to get enough radioactivity to offset its decline with time. From the data for radiolabeling Ceretec with Radiogenix pertechnetate, it became evident that issues could arise due to the lower radioactivity levels and the attendant higher volumes at later time points in the generator's shelf-life. There were also many failures observed for Ceretec kits (stabilized and unstabilized). As well, there were some failures for radiochemical purity for Sestamibi and MAG2 kits. **Investigations to identify the cause led to a volume threshold (Critical Quality Attribute) for each type of kit (anionic, cationic, and neutral) to rectify these issues. A volume limit of 1 mL of RadioGenix Sodium Pertechnetate Tc99m Injection is recommended for reconstituting Ceretec kits, 3.0 mL for Sestamibi kits and MAG3 kits.** CONCLUSION: **Resolved (note the following important issue).**

One issue (raised in the review, Ravi Kasliwal, Ph.D.) was the presence of some H_2O_2 residues in the RadioGenix Sodium Pertechnetate Tc 99m Injection. **This point is important, although it is not clear at this point what its ultimate significance will be, something that will need to be assessed as experience with the generator proceeds.** noting that warnings occur in most of the Tc99m radiopharmaceutical kit directing the user to not use Sodium Pertechnetate Tc 99m Injection that contains any oxidants (or additives, the latter with implication of presence of oxidants), since such substances will oxidize the stannous chloride ($SnCl_2$) to stannic chloride $SnCl_4$, thus depleting the kit of Sn^{2+} , necessary for reduction of $^{99m}Tc^{7+}$ to an oxidation state suitable to radiolabel the ligand in the kit. **Since larger volumes of pertechnetate will contain larger amounts of peroxide, care needs to be given to use as little volume of Sodium Pertechnetate Tc 99m Injection as possible to prevent this interference with radiolabeling Tc99m radiopharmaceutical kits. It is recommended that these directions be incorporated into the labeling.**

Generator Manufacturing -

There was a statement by NorthStar that a drug product post-approval protocol will be performed on one lot annually using the largest ^{99}Mo source size (radioactivity) at a designated nuclear pharmacy, or an authorized testing laboratory. Furthermore, it was stated that the data from these studies will be collected and submitted to the NDA annual

report. There is a post-approval stability protocol and commitment provided in the resubmission. CONCLUSION: **Resolved**.

CDRH:

There were numerous deficiencies identified in DMF #26592 pertaining (1) verification that the Radiogenix generator system meets the requirements for electrical safety, EMC emissions testing and use of RFID wireless technology (medical devices), and (2) performance relating to use of a single pressure sensor, occlusion of flow lines (clogging, kinking) and how performance (**relating to an Overall Critical Quality Attribute**) is affected by aging of the device. The final evaluation (John C. Mcmihael, Ph.D., 01/18/2018) **from the CDRH perspective is approvable with recommendations in a Post-Market Requirement to ensure that the long-term durability of the system is acceptable and the performance of the system does not degrade over time –“ during annual maintenance, check each one of your systems,”** as follows (CDRH review, 01/17/2018):

1. Identify and report all locations of occlusion, clog or deposit buildup in the fluid lines including the valves.
2. Identify and report all locations of leaks in the system.
3. Report any elution radioactivity concentrations which are out of the estimate provided in the software.
4. Report any elution volumes which are out of tolerance.

A letter was received from NorthStar (January 22, 2018), proposing the following schedule milestones for satisfying this PMC”

Draft Protocol Submission: 03/2018
Final Protocol Submission: 08/2018
Study/Trial Completion: 02/2020
Interim/Other: 10/2019
Final Report Submission: 04/2020

The schedule milestones were deemed to be satisfactory (CDRH).

MICROBIOLOGY PRODUCT QUALITY:

There were multiple deficiencies in the application at the end of the first cycle. But, the fundamental issue was the absence of sterilization of the tubing and components after repeated use of the generator in the clinical setting (to **control the Microbiology Product Quality Attributes**), presenting significant risk to patients. In summary, with **implementation of a risk mitigation strategy**, including a mandatory weekly sterilization program, documentation of low bioburden counts in the fluid path, biofilm removal studies (removing early-formed biofilms), in-line depyrogenation, and a final 0.2 µm filter, the risks to patients are controlled considering the complex nature of the RadioGenix System (Jessica Chiaruttini, Ph.D., PQ/OPF/Microbiology). As well, a post-marketing commitment (PMC) to address the safety of long-term use of the System is put into place (managed by DMIP). CONCLUSION: **Resolved (with the PMC)**.

PMC-

Details of the PMC, and dates for completion are as follows (reproduced from the Facsimile from the FDA, dated 01/05/2018. See the next page. In the original facsimile (01/05/2018), it is indicated as a PMR. But, it has been determined to be a PMC, because of the totality of content being CMC (chemistry, microbiology and CDRH).

PMR #1 description:

Evaluate the fluid path bioburden and final product endotoxins and sterility in the RadioGenix system at interim timepoints and the instrument expiry from diverse clinical sites.

PMR Schedule Milestones:

Draft Protocol Submission:	<u>03 /2018</u>
Final Protocol Submission:	<u>04 /2018</u>
Study/Trial Completion:	<u>06 /2019</u>
Interim /Other:	<u>10 /2018</u>
Final Report Submission:	<u>09 /2019</u>

PMR #2 description:

NorthStar will perform studies to evaluate effectiveness of radiolabeling all commercially available technetium Tc 99m drug product kits in the US (except the ones already evaluated in NDA 202158), as per kit manufacturer's directions using representative sodium pertechnetate Tc 99m injection solutions obtained from three different RadioGenix Systems. The studies for each kit will cover different volumes (from low to high end range) of sodium pertechnetate Tc 99m injection solutions obtained throughout the 14-day shelf life of the potassium molybdate Mo 99 source. The effectiveness study must verify that the radiolabeled kits meet the quality requirement listed in the kit manufacturer's package insert. NorthStar agrees to amend the RadioGenix System labeling based on the result of the study, as appropriate.

PMR schedule milestones:

Final Protocol Submission:	<u>04/15/2018</u>
Study/Trial Completion:	<u>04/15/2019</u>
Final Report Submission:	<u>06/15/2019</u>
Other: <u>Interim report</u>	<u>11/15/2018</u>

There was a response from NorthStar (01/12/2018) that they agreed with the PMC and the overall plan of the microbiology post approval study. However, it was noted that in accordance to the current plan there could potentially be a 12-month lag time from instrument (RadioGenix System) installation before the FDA would be aware of any potential problems with bioburden/sterility/endotoxins. The FDA then proposed that NorthStar provide summary information. There would be (1) 3, 6, 9, 12 month samples to evaluate prefiltration fluid path bioburden/endotoxins and final product sterility and endotoxins. (2) 10 instruments would be involved at diverse sites. (3) Trends would be analyzed for potential impact of elution frequency, type of site (hospital, clinic), and duration of use. Summary data would be available 4 months after installation with interim reports every 6 months (March 2019).

Instrument ID	Qualification date (Instrument release date at the site)	Total number of elutions (since installation)	Installation location (City, state)	Installation type (i.e., Hospital, clinic, pharmacy)	Sample Collection Date	Sample collection period (i.e., initial, 3 month, 6 month)	Prefiltration (Blank TPC) sample CFU/mL (TSA results)	Prefiltration (Blank TPC) sample CFU/mL (SDA results)	Prefiltration (Blank TPC) endotoxins/mL (optional)	Sample elution USP<71> sterility results (Sterile/not sterile)	Sample elution endotoxin results (EU/mL)

LABELING:

There have been considerable need for changes in the labeling, that also includes the immediate container for Sodium Pertechnetate Tc 99m Injection USP, vial shield label and the label for the generator itself. The specifics regarding the CMC information in each of these labels is spelled out in the final review of the Drug Product (Ravi Kasliwal, Ph.D.). DMEPA also had comments on the carton and container labels. Requests for this information (including that from CMC, DMEPA and Michele Fedowitz, MD of DMIP) was conveyed to the sponsor on January 12, 2018; this included recommendations for label of the final Product Vial (Collection Vial), the Shield Label, as well as specific comments from DMEPA. It is recommended that the drug label be as follows, based on the history of labeling of the currently approved technetium generators:

RadioGenix™ System (Technetium Tc 99m Generator)
 For production of technetium Tc 99m injection, USP

At this point (01/24/2018), most of the issues for labeling have been resolved. User and Training Manuals have been undergoing current review by CMC, CDRH and Clinical disciplines.

FACILITY INSPECTION STATUS:

All manufacturing facilities involved in the NDA for RadioGenix System are found to be acceptable (Krishnakali Ghosh, Ph.D., OPQ/OPF), 01/12/2018, and with no remaining deficiencies. Those facilities are enumerated in the following table.

University of Missouri Research Reactor, MURR	Receives (b) (4) from NorthStar Medical Radioisotopes & performs QC. (b) (4) are placed in (b) (4) & integrity tested. (b) (4) and released to the NorthStar facility within MURR.
NorthStar Medical Radioisotopes LLC, Columbia, MO	Subdivides the bulk potassium molybdate, into (b) (4) packages and release tested for distribution.
(b) (4)	Performs batch release testing of (b) (4) potassium molybdate
NorthStar Medical Radioisotopes LLC, Madison, WI	Manufactures separation cartridges, initial preparation of (b) (4) at MURR, final QC of the drug injection for release of the RadioGenix System

(b) (4)	Formulates, fills and sterilize packages and labels of the 3 reagent solutions (3% hydroperoxide, 5M potassium hydroxide, and 1.5M sodium acetate)
(b) (4)	Performs bioburden, sterility and cytotoxicity testing. Performs incoming analytical testing and release testing of KOH, sodium acetate and hydroxide reagents.
(b) (4)	Contract manufacturer of populated printed circuit boards and components for the RadioGenix System
(b) (4)	Contract sterilizer. Performs (b) (4) of the packaged primary separation cartridges (ABEC), and sodium acetate reagent

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Sodium Pertechnetate Tc 99m Injection
Non Proprietary Name of the Drug Product	N/A
Non Proprietary Name of the Drug Substance	Sodium Tc 99m Pertechnetate
Proposed Indication(s) including Intended Patient Population	Brain, salivary gland, blood pool, urinary bladder, nasolacrimal draining system imaging, reconstitution of radiopharmaceutical kits
Duration of Treatment	N/A
Maximum Daily Dose	N/A
Alternative Methods of Administration	N/A

D. Biopharmaceutics Considerations

1. BCS Classification: N/A
 - Drug Substance:
 - Drug Product:

2. Biowaivers/Biostudies: N/A
 - Biowaiver Requests
 - PK studies
 - IVIVC

E. Novel Approaches

N/A

F. Any Special Product Quality Labeling Recommendations

N/A

G. Life Cycle Knowledge Information (see Attachment A)

N/A

Risk Assessment - Drug Product (RadioGenix System)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking ¹	Risk Mitigation Approach	Final Risk Evaluation ²	Lifecycle Considerations/ Comments
Identity	N/A	< 25	(b) (4)	< 25	N/A
Radionuclidic Purity	(b) (4) of other isotopes &	25 < RPN < 60	(b) (4)	< 25	N/A

	(b) (4) in ^{99m} Mo (target)		(b) (4)	
Efficiency of extraction of ^{99m} TcO ₄ ⁻ by ABEC	Flow rates (b) (4) ABEC physical characteristics (b) (4)	25<RPN<60	< 25	N/A
Removal of ^{99m} TcO ₄ ⁻ in small volume	(b) (4)	<25<RPN<60	< 25	N/A
Chemical purity of Na ^{99m} TcO ₄	Reagent purity and quality; Kit manufacture; ABEC	<25,RPN<60	< 25	N/A
Performance in radiolabeling kits with Na ^{99m} TcO ₄ (generator eluate)	With generator age, lesser levels of radioactivity output require larger volumes for radiolabeling; presence of peroxide	<25,RPN<60	< 25	N/A
Microbiology Product Quality Attributes ³				
CDRH Product Quality Attributes ⁴				
Manufacturing facility ⁵				

1. RPN (Risk Priority Number)
2. Overall Risk Assessment, RPN < 25 (Low), from a CMC Product Quality perspective.
3. See Microbiology review (01/12/2018) for discussion of the final risk evaluation (Microbiology Product Quality).
4. See reviews for discussion of the final risk evaluation from CDRH perspective (John C. Michael, Ph.D., 01/18/2018).
5. See reviews (01/12/2018) for a complete discussion of the final risk evaluation from the manufacturing perspective (facilities).

Application Technical Lead: Eldon E. Leutzinger, Ph.D., CMC Lead

Eldon E.
Leutzinger -S

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LABELING

I. Package Insert

1. *Highlights of Prescribing Information – This is acceptable*

Item	Information Provided in NDA
Proprietary name and established name - Adequate	RADIOGENIX™ SYSTEM (technetium Tc 99m generator) For the production of sodium pertechnetate Tc 99m injection, USP – as proposed by FDA
Dosage form, route of administration - Adequate	Injection for intravenous, intravesicular, and ophthalmic use
Summary of the dosage form and strength - Adequate	The RadioGenix™ System provides sodium pertechnetate Tc 99m injection, USP, from a non – HEU source of potassium molybdate Mo 99, as a clear, colorless solution containing ^{(b) (4)} mCi/mL to 1153 mCi/mL ^{(b) (4)} to ^{(b) (4)} MBq/mL) of technetium Tc 99m radioactivity in approximately 5mL volume. The amount of Tc 99m radioactivity depends on the radioactivity in the potassium molybdate Mo 99 source. The source is supplied in containers having ^{(b) (4)} Ci (Curie) [^{(b) (4)} Giga-becquerel (GBq)], ^{(b) (4)} Ci ^{(b) (4)} GBq, ^{(b) (4)} Ci ^{(b) (4)} GBq and 6 Ci (222 GBq) activity at the time of calibration. (3)

2. *Section 2 Dosage and Administration – Adequate as amended.*

2.1 Radiation Safety – Drug Handling

- The potassium molybdate Mo 99 source solution and sodium pertechnetate Tc 99m injection are radioactive and should be handled with appropriate safety measures to minimize radiation exposure to patients and healthcare providers. Use waterproof gloves and effective shielding, including syringe shields, throughout the entire preparation and handling for the RadioGenix™ System and technetium Tc 99m injection [see Warnings and Precautions (5.X)].

2.2 Important Administration Instructions

- Use aseptic technique in eluting generator and in all drug preparation and handling.
- Inspect the sodium pertechnetate Tc 99m injection for particulate matter and discoloration prior to administration. Do not administer sodium pertechnetate Tc 99m injection if there is any evidence of discoloration or particulate matter.
- Measure patient dose with a suitable radioactivity calibration system immediately prior to administration. Instruct patients to hydrate after intravenous or intravesicular administration; and encourage the patient to void as soon as the

imaging study is completed and frequently for the next 12 hours to minimize the radiation absorbed dose to the bladder.

- Instruct patients to blow their nose and/or washing their eyes with sterile distilled water or an isotonic sodium chloride solution after ophthalmic administration to minimize the radiation absorbed dose.

(b) (4)



2.3 Recommended Dose for Adults

The recommended doses for adult patients are as follows:

Indication	Megabecquerels	Millicuries	Administration Technique
Vesicoureteral imaging:	18.5 to 37	0.5 to 1	Intravesicular via a urethral catheter Flush the catheter with approximately 200 mL of sterile
Thyroid gland imaging:	37 to 370	1 to 10	Intravenous
Salivary gland imaging:	37 to 185	1 to 5	Intravenous
Nasolacrimal drainage system:	3.7 (max)	0.1 (max.)	Instill with micropipette or similar method

Recommended Dose for Pediatric Patients

The recommended doses for pediatric patients are as follows [See Warnings and Precautions (5.1) and Pediatric Use (8.4)]:

Indication	Megabecquerels	Millicuries (mCi)	Administration Technique
Vesicoureteral	18.5 to 37	0.5 to 1	Intravesicular via a urethral catheter
Thyroid gland imaging:	2.2 to 2.96 per kg (370 MBq max)	0.06 to 0.08 per kg	Intravenous

2.4 RadioGenix System Maintenance

- For complete system maintenance and use follow the RadioGenix™ System Operator Guide (94S05058).
- Install the RadioGenix™ System in an operating environment which complies with local and national requirements for production of radiopharmaceutical products (ISO Class 8 or better environment as described in USP General Chapter 797 Pharmaceutical Compounding – Sterile Preparations).
- The RadioGenix™ System is only for use by trained personnel.
- Only use potassium molybdate Mo 99, processing reagents, saline and other components, including kits [Sterilization Kit (part number 40P05043), Reagent Kit (part number 40P05044), Tc 99m Product Kit (part number 40P05045), Discarded Material Kit (part number 40P05046), and Source Vessel Kit (part number 40P05047)], supplied by NorthStar Medical Radioisotopes.

- Table 3 is a summary of RadioGenix™ System scheduled maintenance and protocol actions. Perform all protocols per the illustrated directions provided in the RadioGenix System Operator Guide (94S05058):

Table 3 RadioGenix™ System Scheduled Maintenance	
Protocol Frequency	Action
Initialize System When Prompted or as needed (host computer screen will prompt the operator to perform initialization)	Perform an initialization cycle when prompted or when RadioGenix™ System is returned to service after a scheduled or unscheduled downtime, such as an interrupted cycle due to equipment or power failure.
Produce Tc 99m Every Elution	Replace the technetium Tc 99m product cartridge, technetium Tc 99 product vial, 0.9% normal saline syringe and the product port caps.
Add/Change Reagents Every Ten (10) Elution or after Sterilization	Replace the primary separation cartridge (PSC), the reagent assembly consisting of 3% hydrogen peroxide, 5M potassium hydroxide and 1.5M sodium acetate along with their port caps.
Add/Remove Source Vessel Fourteen (14) days (maximum) after calibration date	Replace each potassium molybdate Mo 99 source solution with a new Mo 99 source. Use each potassium molybdate Mo 99 source solution by the indicated expiration date on the label.
Sterilization Weekly	Perform software-driven ozonated water system sterilization process Replace the 0.1 micrometer RGX air filter
Exchange Discarded Material Every Two Hundred (200) elution or earlier.	Remove radioactive waste (discarded material) which holds 3.5 liters of discarded material using appropriate safety measures. Replace with a fresh container.

2.6 Directions for Eluting RadioGenix System

- The sodium pertechnetate Tc 99m injection solution is produced using the “Produce Tc 99m” protocol through the RadioGenix™ System home screen. **Follow step by step directions for use provided in the RadioGenix™ System Operator Guide (94S05058).**
- The elution process to produce sodium pertechnetate Tc-99m injection involves the initial installation and set-up of the equipment, reagents, sterilizing filters, and sterile final product collection vials provided by NorthStar Medical Radioisotopes [see Table 3]
- Implement the following prerequisites before the “Produce Tc 99m” protocol is initiated:
- Connect the potassium molybdate Mo 99 source container using the Source Vessel Kit (part number 40P05047)

- Aseptically install the RadioGenix Reagent Kit (part number 40P05044) consisting of 3 reagent solutions (3% Hydrogen Peroxide, 5M Potassium Hydroxide, and 1.5M Sodium Acetate) and the primary separation cartridge (PSC).
- Aseptically assemble and install the technetium Tc 99m Product Kit (part number 40P05045) consisting of an alumina column, 0.22-micron filter, and a 20mL sterile collection vial.
- Attach the supplied pre-filled syringe containing 0.9% sodium chloride injection USP to the saline port.
- Initiate the computer controlled elution process to prepare sodium pertechnetate Tc-99m injection.
- After delivery of the sodium pertechnetate Tc 99m injection to the collection vial is complete, remove the collection vial and perform the quality control procedures [see *Dosage and Administration (2.7)*].

2.7 Quality Control of Sodium Pertechnetate Tc 99m Injection

Perform the following quality control procedures on each sodium pertechnetate Tc 99m injection prior to its release for clinical use or for reconstitution with Tc 99m radiopharmaceutical kits.

Mo 99 Breakthrough Test

- Using a suitable radioactivity calibrator, determine the activity of technetium Tc 99m eluted.
- Place the sodium pertechnetate Tc 99m injection eluate in a calibrated Mo 99 assay shield. Place lid on container and put the entire container in the dose calibrator chamber.
- Record the activity of molybdenum Mo 99 on the most sensitive scale.
- Divide the activity of molybdenum Mo 99 by the activity of technetium Tc 99m. Correct for decay and shielding effect, if necessary.
- Determine the molybdenum Mo 99/technetium Tc 99m ratio at the time of elution and from that ratio, determine the expiration time of the eluate. Each sodium pertechnetate Tc 99m injection eluate must meet or exceed purity requirement of 0.15 microCi of Mo 99 per milliCi of Tc 99m.
- The expiry time for each eluate of sodium pertechnetate Tc 99m Injection must be **no later than the 12 hours post elution or the time where the Mo 99 to Tc 99m ratio reaches 0.15 microCi/mCi, whichever occurs first.**

Colorimetric Aluminum Ion Test Procedure

- Using an aluminum ion indicator kit, determine the aluminum ion concentration of the eluate per the manufacturer's instructions.
- The eluate concentration must not exceed 10 micrograms/mL.

Determination of pH

- Place a small drop of Sodium Pertechnetate Tc-99m Injection on a colorimetric pH strip.
- Examine and compare the coloration of the test strip with the colors displayed on the pH cartridge.
- The pH range must be between 4.5 and 7.5.

Radiolabeling (Reconstitution) of Kits

- (b) (4)
[REDACTED] In general, use no more than 3 mL volume. For radiolabeling certain kits (such as Kit for the preparation of technetium Tc 99m exametazine), use no more than 1 mL volume.

[REDACTED] (b) (4)

3. Section 3 Dosage Forms and Strengths

[REDACTED] (b) (4)

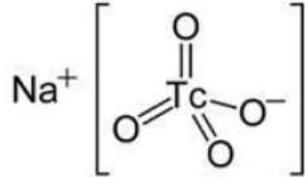
4. Section 11 Description (acceptable as amended)

The RadioGenix™ System provides sodium pertechnetate Tc 99m injection, USP for intravenous use, intravesicular use, ophthalmic use, or for preparing radiopharmaceutical kits. The RadioGenix™ System uses a non-Uranium/(b) (4) potassium molybdate Mo-99 source solution to produce sodium pertechnetate Tc 99m Injection, USP. The RadioGenix™ System uses potassium molybdate Mo 99 sources at activities of $\frac{(b)(4)}{(4)}\text{Ci}$ to 6 Ci/29 mL $\frac{(b)(4)}{(4)}\text{GBq}$ to 222 GBq) at the date and time of calibration.

Elution of RadioGenix™ System produces sodium pertechnetate Tc 99m ($\text{Na}^{99\text{m}}\text{TcO}_4$) in approximately 5 mL of sterile 0.9% sodium chloride injection solution. The activity of sodium pertechnetate Tc 99m produced varies $\frac{(b)(4)}{(4)}\text{mCi/mL}$ to 1153 mCi/mL of

technetium Tc 99m) and depends on the activity of potassium molybdate Mo 99 present in the source container originally, the decay time since the calibration time and the elapsed time since the previous sodium pertechnetate Tc 99m elution.

Sodium pertechnetate Tc 99m is an inorganic compound with the formula $\text{Na}^{99\text{m}}\text{TcO}_4$. In solution, sodium pertechnetate exists as dissociated Na^+ cations and pertechnetate TcO_4^- anions with the following molecular structure:



The eluted sodium pertechnetate Tc 99m injection, USP is sterile, non-pyrogenic, clear and colorless solution. The pH of the solution is between 4.5 and 7.5.

5. Section 16 How Supplied/Storage and Handling

16.1 How Supplied

The RadioGenix™ System is a Technetium Tc 99m Generator supplied and installed by Northstar Medical Radioisotopes. It produces sodium pertechnetate Tc-99m injection from a non-uranium potassium molybdate Mo 99 source solution. The potassium molybdate Mo 99 source solution is shielded within a source container which completely encases a vial that contains 29mL of solution. NorthStar supplies (b) (4) potassium molybdate Mo-99 solutions with the referenced calibration date and time specified on the container label:

Table 11 Potassium Molybdate Mo 99 Solution Containers			
Mo 99 Activity at Time of Calibration		Product Number	NDC Number
Curies	Gigabecquerels		
6.0	222	40P03246	XXXXXX-XXX-XX

(b) (4)

The following kits are used in the operation of the RadioGenix™ System as described in the RadioGenix™ Operator Guide, 94S05058, section titled, “RadioGenix™ System Tc 99m.

Table 12 Materials Supplied in RadioGenix Source Vessel Kit, part number (p/n) 40P05047

Component Description	Component Part Number	Qty.
Catheter (b) (4)	77P03046	1
Air filter	77C01237	1
Manifold	12D02774	1
Absorbent Cloth	73C05400	1
Black Cap	77C01489	1
(b) (4) (Cap)	77C05450	1
Luer Cap	77C05449	1

Table 13 Materials Supplied in RadioGenix Reagent Kit, p/n 40P05044

Component Description	Component Part Number	Qty.
(b) (4) (Reagents)	16P04143	1
Primary Separation Cartridge (PSC)	40P03354	1
(b) (4)	16C04989	3

Table 14 Materials Supplied in RadioGenix Tc-99m Product Kit, p/n 40P05045

Component Description	Component Part Number	Qty.
Tc-99m Product Cartridge	40P04600	1
Collection Vial	77C01318	1
Saline Syringe	16C05227	1
(b) (4) (Product port cap)	16C05212	1
(b) (4)	16C04989	1

Table 15 Materials Supplied in RadioGenix Sterilization Kit, p/n 40P05043

Component Description	Component Part Number	Qty.
Primary Separation Cartridge (Blank)	40P04578	1
Tc-99m Product Cartridge (Blank)	40P05377	1
(b) (4) (Spike) (b) (4)	-	-
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Air Filter	77C01237	1
(b) (4)	16C04989	12
(b) (4) (Product port cap)	16C05212	1
Purge Container (b) (4)	77C05585	1
SWFI - (b) (4)	16C04488	1

Table 16 Materials Supplied in RadioGenix Discarded Material Kit, p/n 40P05046

Component Description	Component Part Number	Qty.
Discarded Material Container	12D05146	1
Cap and Tube Assembly	-	-
Tube	77C05431	7"

Luer Cap	77C05449	1
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16.2 Storage and Handling

Storage

- Receipt, transfer, storage, handling, possession or use of the potassium molybdate Mo-99 source solution, sodium pertechnetate Tc-99m injection, and radioactive components of the RadioGenix™ System are subject to the radioactive material regulations and licensing requirements of the U.S. Nuclear Regulatory Commission, Agreement States or Licensing States.
- Install and operate RadioGenix™ System generator at [REDACTED] (b) (4) 20° to 25°C (68° to 77°F).
- Store Potassium Molybdate Mo 99 source solutions at [REDACTED] (b) (4) 20° to 25°C (68° to 77°F).
- Store the Sterilization Kit (p/n 40P05043), Reagent Kit (p/n 40P05044), and Tc-99m Product Kit (p/n 40P05045), [REDACTED] (b) (4).

Disposal

- When the potassium molybdate Mo 99 source has reached the end of its useful life or expiration date, remove the source vessel from the RadioGenix™ System and return to NorthStar for processing.
- Dispose the waste (discarded material) container in accordance with applicable regulations.
- The maximum use period of a RadioGenix™ System is one year from the date of installation. After expiry, have Northstar refurbish and recertify the RadioGenix™ System.

Reviewer's Assessment of Package Insert: *Adequate*

The package insert (as revised in concert with the Division of Medical Imaging) includes considerable complex information for this complex generator drug product, and is satisfactory.

II. Labels:

1. *Container and Carton Labels*

The applicant has not provided the labels for the final product vial (collection vial) where the sodium pertechnetate Tc 99m injection solution is collected. The secondary carton (the label that is placed on the shield) is also not provided. The applicant should be asked to provide these labels. The labels should include all the necessary information, including:

- Name and route of administration:
 - **Sodium Pertechnetate Tc 99m Injection**
 - for intravenous, intravesicular, and ophthalmic use
- Strength statement:

- Contains – XXX mCi at YYY time (in the vial label a predetermined range at calibration time may be printed, but the outer container should have the written determined amount and the time of assay).
- Quantitative composition (active and inactive ingredients and amounts).
- Lot Number (should be written on the shield label).
- Expiry Date (the vial label may state expires in 12 hours from the time of calibration, while the shield label should have the expiration date / time written on it).
- “Rx Only” statement.
- NDC number
- Storage conditions statement.
- Bar Code, Radiation symbol.
- Non-HEU source statement
- Name and address of the manufacturer.

2. Label for the Generator:

The approved product is a generator, and should have a label placed on it. The labels should include all the necessary information, including:

- Name and route of administration:
RADIOGENIX SYSTEM (technetium Tc 99m generator)
For the production of sodium pertechnetate Tc 99m injection, USP
- Strength statement:
For use with (b) (4) 6 Ci (222 GBq), at calibration, Potassium Molybdate Mo 99 sources.
 - Lot Number (should be written on the shield label).
 - Date of installation (i.e., final certification)
 - Expiry Date (e.g., expires in 1 year from the date of installation).
 - NDC number
 - Storage conditions statement (e.g., Install and use at controlled room temperature). Statement regarding the environmental conditions for installation and use.
 - Bar Code, Radiation symbol.
 - Name and address of the manufacturer.

3. Potassium Molybdate Mo 99 source vessel label:

Following label is provided:



Comments:

- Move manufacturer logo towards the bottom of the label.
- Revise the name of the source to “Potassium Molybdate Mo 99 Source for RadioGenix™ System” and place it in bold on the top side.
- Delete (b) (4) and insert statement in the Caution statement “For use with RadioGenix™ System only. Not for Direct human administration.”
- In addition to the picture for storage, there should be a clear statement “Store at Controlled room temperature 20°C – 25°C (68°F -77°F). Include this statement on the right panel.
- Include a composition statement “Contains Potassium Molybdate Mo 99 in 5M potassium hydroxide solution” on the right panel under the name of the product.

Reviewer’s Assessment of Labels: *Inadequate (pending at this time)*

The applicant has not provided labels for immediate container (in which sodium pertechnetate Tc 99m injection product is collected), the vial shield label (carton label), and the label for the generator. The labels should be requested and the associated comments should be sent to the applicant. Comments regarding the labels for the other generator associated kits and sources should also be sent to the applicant.

List of Deficiencies:

1. You did not provide label(s) for the generator. Provide label for the generator that should include all the necessary information, including:
 - Name and route of administration:

RADIOGENIX™ SYSTEM (technetium Tc 99m generator)
For the production of sodium pertechnetate Tc 99m injection, USP
 - Strength statement:

For use with (b) (4) 6 Ci (222 GBq), at calibration, Potassium Molybdate Mo 99 sources.

 - Lot Number (should be written on the shield label).
 - Date of installation (i.e., final certification)
 - Expiry Date (e.g., expires in 1 year from the date of installation).
 - NDC number
 - Storage conditions statement (e.g., Install and use at controlled room temperature). Statement regarding the environmental conditions for installation and use.
 - Bar Code, Radiation symbol.
 - Name and address of the manufacturer.

2. You did not provide the labels for the final product vial (collection vial) where the sodium pertechnetate Tc 99m injection solution is collected, and the shield label. Provide these labels. The labels should include all the necessary information, including:
 - Name and route of administration:

- **Sodium Pertechnetate Tc 99m Injection**
 - for intravenous, intravesicular, and ophthalmic use
 - Strength statement:
 - Contains – XXX mCi at YYY time (in the vial label a predetermined range at calibration time may be printed, but the outer container should have the written determined amount and the time of assay).
 - Quantitative composition (active and inactive ingredients and amounts).
 - Lot Number (should be written on the shield label).
 - Expiry Date (the vial label may state expires in 12 hours from the time of calibration, while the shield label should have the expiration date / time written on it).
 - “Rx Only” statement.
 - NDC number
 - Storage conditions statement.
 - Bar Code, Radiation symbol.
 - Non-HEU source statement
 - Name and address of the manufacturer.
3. Revise the potassium molybdate Mo 99m source vessel label as follows and submit the revised label:
 - Move manufacture logo towards the bottom of the label.
 - Revise the name of the source to “Potassium Molybdate Mo 99 Source for RadioGenix® System” and place it in bold on the top side of the right panel.
 - Delete (b) (4) and insert statement in the Caution statement “For use with RadioGenix System only. Not for direct human administration.”
 - In addition to the picture for storage, there should be a clear statement “Store at Controlled room temperature 20°C – 25°C (68°F -77°F). Include this statement on the right panel.
 - Include a composition statement “Contains Potassium Molybdate Mo 99 in 5M potassium hydroxide solution” on the right panel under the name of the product.
 4. In the PSC Labels (the component and box label),
 - the name of the component should be made prominent.
 - The Name should be “Primary Separation Cartridge (PSC) for RadioGenix System”.
 - The name and address of the Manufacturer (NorthStar) should be less prominent and be placed towards the bottom of the label.
 - In addition to the picture for storage, there should be a clear statement “Store at Controlled room temperature 20°C – 25°C (68°F -77°F).
 5. In the TPC Labels (the component and box label),
 - the name of the component should be made prominent.
 - The Name should be “Technetium Tc 99m Product Cartridge (TPC) for RadioGenix System”.
 - The name and address of the Manufacturer (NorthStar) should be less prominent and be placed towards the bottom of the label.
 - In addition to the picture for storage, there should be a clear statement “Store at Controlled room temperature 15°C – 30°C (59°F -86°F).



Ravindra
Kasliwal

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MICROBIOLOGY

Product Background:

NDA: 202158

Drug Product Name / Strength: RadioGenix System (Sodium Pertechnetate Tc 99m Injection USP)/ 6 Curies per system

Route of Administration: Intravenous injection and installation

Applicant Name: NorthStar Medical Radioisotopes, LLC

Manufacturing Site: Multiple. See Section P.3.1 on page 7.

Method of Sterilization: Sterile filtration

Review Recommendation: Recommended for approval

Review Summary: The complex nature of this product control strategy does not allow a high-level summary in this section. An overall risk assessment for the RadioGenix system is found on the second to last page of this review and incorporates the data summarized in this document. Briefly, the complex, paradigm shifting application was deemed acceptable from a product quality microbiology standpoint. Risk mitigation strategies evaluated here include a weekly ozone sterilization process, validated depyrogenation processes for the fluid path, maintenance of a low bioburden fluid path, and inclusion of a (b) (4) sterilizing filter for each patient dose. Additional supporting studies were provided and are evaluated here. A post-marketing commitment to address the safety of the long-term instrument use was issued and is being managed by the Division of Medical Imaging Products.

List Submissions Being Reviewed: 08 May 2017, 01 June 2017, 03 October 2017, 13 October 2017, 01 November 2017 (Seq. 0032), 08 December 2017

OND managed all sponsor communications and information requests. A teleconference with the sponsor on 20 July 2017 discussed the replacement of (b) (4) with a new manufacturer ((b) (4)) for the reagent bags. A face to face meeting with the sponsor on 17 November 2017 included a demonstration of the RadioGenix instrument. A teleconference with the sponsor on 05 December 2017 provided clarification on the 20 November 2017 microbiology information request. Filing microbiology review comments were addressed in the 01 June 2017 amendment. The 13 October 2017 amendment replaced the original reagent bag manufacturer with (b) (4). An information request with twelve microbiology comments was sent to the applicant on 13 October 2017 and a

response was received on 01 November 2017 (Seq. 0032(33)). A second information request was sent on 20 November 2017 and the response was received on 08 December 2017. The information requests and responses are incorporated into the relevant sections of this review.

Highlight Key Outstanding Issues from Last Cycle: [REDACTED] (b) (4)

[REDACTED] Multiple other deficiencies were noted. This submission describes a new instrument and this review does not rely on any data described in the original microbiology review dated 30 May 2013 in DARRTS. Multiple meetings were held with the applicant during the initial review cycle (filed under the NDA) and after the Complete Response letter (filed under the NDA and IND 109871).

Remarks: This is a Class 2 resubmission for a 505(b)(2) NDA with a 3-month extension of the PDUFA clock. The submission contains duplicate reports and protocols in Module 3. Unless otherwise indicated, the final report, but not all final protocols, were reviewed by this reviewer.

Concise Description Outstanding Issues Remaining: A post-marketing commitment accompanies this review. The PMC is managed by DMIP and a description of the rationale and study design may be found on page 55 of this review.

Supporting Documents: [REDACTED] (b) (4) was found adequate in the 12 August 2013 microbiology review submitted to BIRAMS.

S Drug Substance

The potassium molybdenum Mo-99 drug substance is sterilized during drug product manufacture and no review of the drug substance will occur here. The Mo-99 source is exchanged every other week and is provided in 5 M potassium hydroxide (KOH).

P.1 Description of the Composition of the Drug Product

The RadioGenix instrument (described below) is used, in combination with sterile and non-sterile consumables, to produce sterile Tc99m for injection. The RadioGenix instrument is installed at each nuclear pharmacy/clinical site by NorthStar personnel.

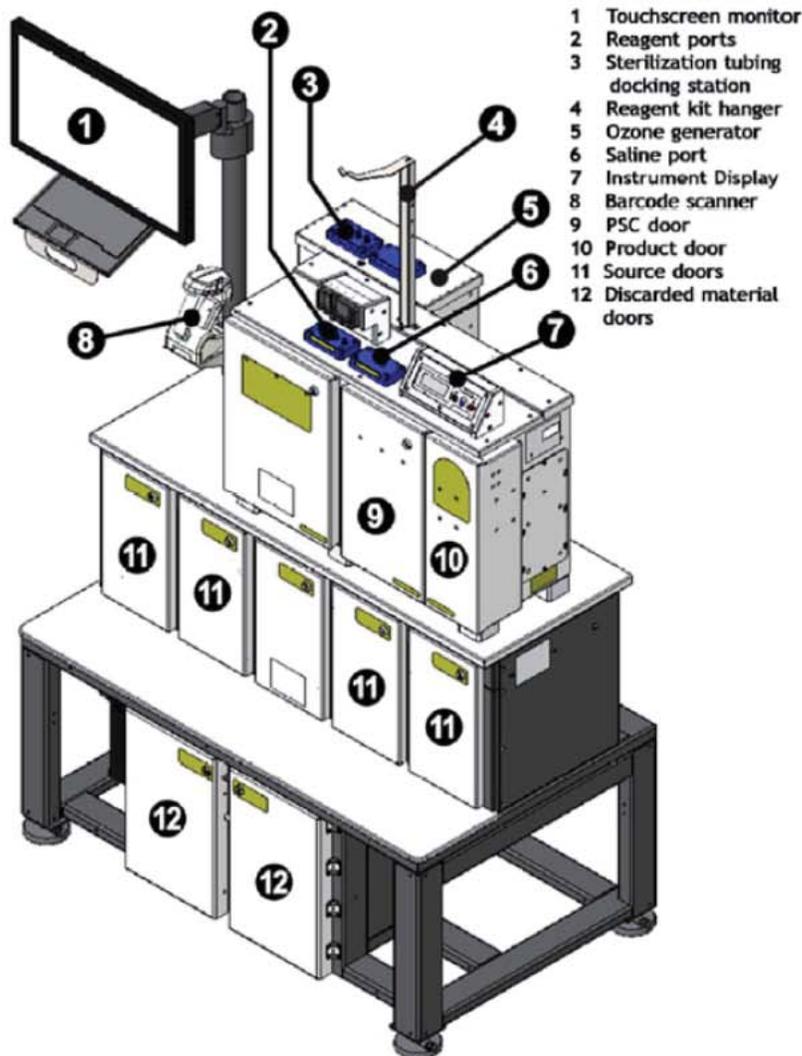
- **Description of drug product** – The drug product is a sterile solution with a concentration of [REDACTED] (b) (4) in a 20 mL glass vial.
- **Drug product composition** –

Table 1- Drug product composition (Sponsor Table 1 Module 3.2.P.1)

Component	Concentration (mCi/mL)	Amount per Vial (Elution)	Function
Na ^{99m} TcO ₄	(b) (4)	(b) (4)	Active pharmaceutical ingredient
NaCl	(b) (4)	(b) (4)	(b) (4)
Water for Injection	(b) (4)	(b) (4)	(b) (4)

- Description of container closure system** – 20 mL (b) (4) glass vials, (b) (4) stopper and (b) (4). The sterile empty vials are supplied by (b) (4) (b) (4) and are item 77C01318.
- Description of the RadioGenix (RGX) System** – The instrument and reagents are supplied by NorthStar and are part of a complex software-driven system. The sterile bagged reagents are exchanged every 10 elutions or once a week and include 0.9% sodium chloride injection, 3% hydrogen peroxide, 5M potassium hydroxide, and 1.5 M sodium acetate. The sterile reagents are supplied in (b) (4) bags with tubing and connectors and the 3 bags are assembled into a reagent module (item 16P04143). The 5M KOH bag is part 16P04147, the 1.5 M sodium acetate is part 16P04146, and the 3% H₂O₂ is part 16P04145. The generator tubing, valves, and pumps are exchanged (b) (4) by NorthStar staff. The primary separation cartridge is exchanged every 10 elutions or weekly. The sterile saline syringe, Tc99m product cartridge (with 0.22 µm filter) and product vial are exchanged with every elution. The ozone generator is replaced every 6 months (Module 3.2.P.3.5 page 78/102). The product fluid path is shown in Figure 2 below and most of the fluid path is located within the top three doors shown in Figure 1.

Figure 1- RadioGenix System (Sponsor Figure 17 Module 3.2.P.3.3)



- **Description of the associated consumable kits-** Multiple kits are provided by NorthStar and these kits are required for use of the RGX. The sterilization information for the kits is provided on page 50 of this review.

Table 2- List of associated kits and their components

Kit Name	Replacement Schedule	Components (* indicates sterility)	Reference
Source Vessel Kit	2 weeks	Mo99 source vessel, shipping cap, crimp/cut tool, 1.5 mm hex tool, catheter, air filter (*), manifold	3.2.P.3.3 Figure 8 & 9
Source Vessel Consumables Kit	“periodically”	Catheter, air filter (*), manifold, Luer cap (*), Cap (*), black cap, absorbent cloth	Operator Guide Figure 85
Reagent Kit	10 elutions (max 7 days)	Reagents (*), hydrogen peroxide wipes (*), primary separation cartridge (PSC) (*)	3.2.P.3.3 Figure 10
Tc99m Product kit	1 elution	Tc99m collection vial (*), Tc99m product cartridge (TPC) (*), saline	3.2.P.3.3 Figure 11

		syringe (*), product port cap (*), cap (*), hydrogen peroxide wipes (*)	
Sterilization Kit	Every 7 days	Discarded water container, air filter (*), blank PSC (*), blank TPC (*), product vial, sterile water for injection (SWFI) (*), spike (*), product port cap (*), Caps (*), hydrogen peroxide wipes (*)	Operator Guide Figure 105 and Module 3.2.P.3.3. Figure 20
Discarded Materials Kit	Every 200 elutions	Luer cap (*), discarded material container, silicone tubing	Operator guide Figure 153

Reviewer’s Assessment: *{Adequate}* The description of the instrument and components is adequate to allow a sterility assurance evaluation. The majority of the RadioGenix functional and chemical evaluation can be found in the CMC and CDRH reviews and is beyond the scope of this review. This review includes sterility assurance concerns only and CMC and CDRH were consulted by this reviewer for ozone stability, fluid velocity concerns, and evaluation of instrument faults.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity

Multiple sterile barriers are required for effective use of the RadioGenix system and the associated components. These include the final 20 mL vial, sterile reagent bags, and multiple sterile components in the supplied kits. The overpackaging for each kit is not a (b) (4) and some sterile components are multi-use and will not necessarily maintain sterility over the in-use period. The use/reuse period for each component is provided in Table 2. A list of components in each kit can be found in Module 3.2.P.3.3 and is provided in Table 2 of this review. Sterile components (filter, caps, luer caps, etc.) will not be evaluated for the outer packaging maintenance of sterility as this is normally outside of the scope of the product quality review and these components will not maintain sterility over the in-use duration. (b) (4) and released by NorthStar directly to the end user. The sterile saline syringe and sterile WFI bags are cleared 510k products and will not be addressed further. Sterilization information for components can be found on page 50 of this review.

The 20 mL vial container closure integrity studies are covered in (b) (4) and were deemed acceptable.

Report PQ4282 in Module 3.2.P.3.3 (13 October 2017) contains seal integrity test results from reagent bags sealed at (b) (4) using the (b) (4). (b) (4) were tested by applying (b) (4) and visually inspected for the presence of (b) (4). Excess tubing from engineering batch #170720 (b) (4) reagent bags was used for testing. Air

was applied and the seal was submerged in water and visually inspected for bubbles. No bubbles were noted and no deviations were observed.

Reviewer's Assessment: *{Adequate}* The 20 mL glass vial will be integral at the time of receipt and used within 12 hours of the elution. The reagent bag seal at the current manufacturer was adequately verified under pressure conditions. The bags remain in use for up to 7 days and studies on page 42 of this review summarize data that demonstrate that none of the reagents support microbial growth during the 7 day in use period. Those studies also demonstrate that the single use saline syringe (510k product) does not support growth beyond the 1 day maximum use time.

Antimicrobial Effectiveness Testing

Antimicrobial effectiveness testing is not required. The drug product does not contain a preservative and expires 12 hours after elution.

P.3 Manufacture

P.3.1 Manufacturers

Table 3- Manufacturers applicable to the sterility assurance review

Manufacturer	Process/responsibility
(b) (4)	Analytical chemical and microbiological testing. Endotoxins release testing for KOH reagent bags. Associated with the (b) (4) site. Reagent bag release testing (b) (4) of the primary separation cartridge ABEC, Tc99m product cartridges, and acetate reagent Manufacture of the (b) (4) used for elution of the final patient dose. The (b) (4) is assembled with the (b) (4) cartridge at NorthStar and (b) (4) at (u) (4)
NorthStar Progress Rd Operations 3060 Progress Road Madison, WI 53718	Manufacture of primary and secondary cartridges, assembly of tubing catheters and vials, assembly of the consumable kit, final release of the RadioGenix instrument
NorthStar Femrite Facility 5249 Femrite Road Madison, WI 53718	Installation and release of the RadioGenix instrument at the customer site. Training of the installation site staff. Conduct of endotoxins testing (not done commercially for release).
(b) (4)	Reagent bag manufacturing and release testing

(b) (4) (b) (4) manufactures the box and electronics but does not assemble the tubing. Other manufacturers not directly related to this review are not listed here.

Reviewer’s Assessment: *{Adequate}* The manufacturers and their associated activities were adequately described.

P. 3.3 Description of the Manufacturing Process and Process Controls

Overall Manufacturing Operation

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Reviewer's Assessment: *{Adequate}* The sterilization information in the table above is acceptable. The sterile hydrogen peroxide wipes and sterile caps were not supported by full sterilization validation information. However, these components are not part of the product fluid path and are used for bioburden control. As such, complete information is not required here.

P.5 Control of Drug Product

The only product quality microbiology release testing of patient dosage forms is the filter integrity test described on page 10 above. The application describes release testing for the RadioGenix instruments and final quality control testing conducted prior to patient administration at the elution site.

P. 5.1 Specification

Before releasing each instrument, NorthStar will conduct sterility and endotoxins analysis on a single elution.

Requirement Description	USP Specification	USP Test Protocol	NMR Test Procedures	Contract Test Lab Test
Performed by NorthStar QC or Qualified Test Laboratory				
Sterile Solution	No Growth of microorganisms over 14 days	USP General Chapter <71> (also refer to USP General Chapter <1211>)	75T03209	NSIP-9
Radionuclide Identification	Gamma ray spectrum w/ Tc- 99m major photo peak = 0.140 MeV	USP Monograph Sodium Pertechnetate, Tc 99m Injection or accepted equivalent	75T07154 75Q07155	NSIP-1
Bacterial Endotoxins	<25 EU/mL (≤ 175/V USP EU/mL of Injection when compared with USP Endotoxin Reference Standard)	USP General Chapter <85> or accepted equivalent	75T03208	NSIP-3

Reviewer’s Assessment: *{Adequate}* The control strategy for the drug product relies on the sterilizing filter, weekly sterilization process, and closed (low bioburden) fluid path. The lack of sterility and endotoxins release testing for each dose is acceptable and the supporting rationale was described throughout this review and is summarized on the last page of this review.

P.5.2 Analytical Procedures

Not applicable. The filter integrity test is described on page 10 of this review.

P.5.3 Validation of Analytical Procedures

Not applicable.

P.7 Container Closure

See page 2 of this review.

P.8 Stability

Traditional stability studies are not applicable to this drug product. The elution is stored for not more than 12 hours prior to patient administration. A post-approval commitment will evaluate the microbiological control of the RadioGenix system during the proposed 12 month shelf life.

A Appendices

Not applicable.

R Regional Information

Executed Batch Records

Batch records were provided but not reviewed. The elution report was reviewed and addressed in the 20 November 2017 information request.

Comparability Protocols

No comparability protocols were provided in the submission.

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A.

Package Insert

The package insert does not contain complete information needed to safely elute Tc99m. The detailed information is provided in the Operator Guide, which was reviewed and is described below. The PI allows a 12 hour hold time from the end of an elution, through compounding with Tc99m kits, and final patient administration. This is standard practice for radiopharmaceuticals and no additional information will be requested.

- **Post-dilution/constitution hold time** Not applicable.

Operator Guide

The RadioGenix System Operator Guide is document 94S05058 and the applicant references the Operators Guide for detailed information on the system. The Guide will be used for training and routine operations. The Operators Guide was reviewed and comments were sent to the applicant through the OND Labeling Reviewer, but are not included in this review. See the labeling review for more information.

Information request dated 13 October 2017 (Comment #16 from the response)

Define any maximum “downtimes” permitted for the instruments. For example, if an instrument sits unused at a facility for 6 months, is there a different process for restarting use besides the weekly ozonation and reagent replacement? Is this restart process built into the software, if applicable?

Summary of the 01 November 2017 response

The internal NorthStar policy is not more than (b) (4) downtime but this time period is not specified in the Operator’s Manual. The Operator’s Manual simply states that long-term storage is not part of the instruments intended use and that the user should contact NorthStar before attempting to store the instrument or before starting use again after a storage period. The restart procedures are defined in 94S07821 Rev 00 page 50. A rinse is conducted to confirm that no salt residues have built up and occluded the instrument. The annual PM is in the same document beginning on page 155 and includes (b) (4)

The installation of the fluid path will occur at the customer site and in an ISO 8 environment.

Information request dated 13 October 2017 (Comment #17 from the response)

The insertion of the sterile spike into the sterile product vial is downstream of the product sterilization step (0.22 µm filter) and must be conducted aseptically. Describe the risk of and the risk mitigation strategy in place to prevent users from touching the spike to the side of the non-sterile lead shield. Provide a description of the microbial control strategy for the lead shield placed over the product collection vial prior to the insertion of the sterile Tc99m product cartridge (TPC).

Summary of the 01 November 2017 response

The tungsten (not lead) shield restricts the needle movement and once the sterility filter enters the shield the needle will not be able to touch the shield. This was evaluated during the 17 November 2017 demonstration at White Oak and was found acceptable.

Reviewer's Assessment: *{Adequate}* The PI and Operator's Guide were reviewed and found acceptable, pending the revisions provided to the OND labeling reviewer. The ISO8 environmental requirement was discussed with the applicant at the 17 November 2017 face to face meeting with the applicant. The practicality and feasibility of the requirement was discussed and NorthStar plans to verify the ISO8 environment prior to instrument installation. The Agency agrees that the controlled environment minimizes risks to the product fluid path.

Post-Approval Commitments:

Comment provided to the applicant in the mid cycle communication letter:

The Agency acknowledges the significant improvements in the sterility assurance program associated with the RadioGenix instrument in the NDA resubmission. While the full review process is on-going, the Agency is considering a post-marketing commitment to evaluate the microbiological quality of instruments during the 12-month shelf life. While the specific studies potentially needed are still under review, we envision that these studies would utilize equipment from clinical sites to improve the understanding of the microbial colonization of equipment under in use conditions. Data collected from this study will be used to support the 12-month expiry and any potential reuse of the (b) (4) valves. No response is required at this time; this information is provided for your consideration.

Post approval commitment rationale and high level study design (copied from PMC template provided to OND on 22 December 2017)

The PMC will evaluate the fluid path bioburden and final product endotoxins and sterility in the RadioGenix instrument at interim timepoints and the instrument expiry from diverse clinical sites.

Rationale- The RadioGenix instrument will be installed in radiopharmacy clinical sites and is a sterile manufacturing system intended for use outside of a traditional cGMP manufacturing environment. The instrument is paradigm shifting with respect to aseptic manufacturing and no similar products are available for comparison. The bioburden control, endotoxins control, and sterilization efficacy have not been evaluated after use in a clinical setting as there is no active IND clinical study for this NDA. Completed successful sterilization validation studies and bioburden control data were generated during product development but the clinical use poses potential risks that can only be evaluated with a post-marketing study. This study is designed to document that the instruments maintain a low bioburden product fluid path and produce sterile, non-pyrogenic patient doses at expiry of the ozone generator and the RadioGenix instrument. If interim results demonstrate that the instrument is not in a state of microbiological control, the Agency may reduce the instrument expiry.

Study design- The risk for elevated bioburden in the RadioGenix instrument increases as the time post-installation increases due to continued exposure to environmental microorganisms. The risk to patients is controlled with the ozonation cycle and the inclusion of a 0.22-micron sterilizing filter; however, more data are needed on microorganisms recovered in the pre-filtration fluid path during use. Time points should include 3, 6, 9, and 12 month evaluations at a minimum of 10 RadioGenix instrument sites for each time point. Interim reports are required within approximately 1 month of each time point to identify any potential patient safety concerns. The same instrument sites should be used for the study duration, if possible. If preliminary data (i.e., 3 and 6 months) suggest no increases in bioburden or endotoxins, then subsequent locations/timepoints may be reduced after discussion with the Agency. Fluid path bioburden and endotoxins testing on unfiltered samples should be evaluated after the maximum time (i.e., 6-7 days depending on clinical site practice) post-ozonation. Endotoxins and sterility testing should be evaluated on production samples eluted by the clinical site staff after the maximum time (i.e., 6-7 days depending on clinical site practice) post-ozonation. It is unknown whether the greatest microbiological risk is posed from high use or low use clinical sites so the number of elutions conducted with each instrument should be provided for each clinical site. The Agency expects the results submitted in interim reports to include the number and type (genus and species, where possible) of microorganisms recovered. Optional, but useful, studies would evaluate biofilm formation in the tubing and (b) (4) valves at instrument expiry. Biofilm studies at expiry may be required if the microbiological data recovered at interim time points suggest that excessive increases in bioburden in the fluid path are due to biofilm formation.

Reviewer's Assessment: The PMC is still under development at the time of completion of this review. This review recommendation for approval is dependent on the approval and implementation of the above study and interim analyses will be required to support the safe use of the RadioGenix system.

List of Deficiencies: None

Primary Microbiology Reviewer Name and Date: Jessica Chiaruttini, PhD; 26 December 2017

Reviewer's Final Assessment: *The Agency recognizes that the RadioGenix system is not a traditional aseptic manufacturing environment and requires considerable flexibility in the established regulatory paradigm for sterile drug manufacturing. The FDA Guidances, PDA Technical reports, and other published materials available in the literature are difficult to apply to the system proposed here. This application required an unprecedented synthesis of data provided from individual studies as no single study could be conducted that would answer all of the microbiology questions posed by the RadioGenix. This reviewer has consulted repeatedly with expert reviewers within DMA to elicit a consensus on acceptable standards for this NDA. The complex nature of the system and the control program's reliance on multiple overlapping components required*

a comprehensive evaluation and risk assessment. This reviewer believes that the risks to patients have been controlled to the extent possible with the system design. There are no remaining fundamental flaws present in the RadioGenix, as understood by this reviewer. The novel ABEC resin that allows for concentration of the Tc99m from a low enriched molybdenum source is a critical leap forward in the Tc99m radiopharmaceutical technology (per the CMC review staff). As such this system is designated as a high priority application for both the FDA and the Department of Energy. The potential risk to patients was weighed against the scientific and manufacturing procedures proposed here. While a post-marketing study was deemed necessary to address some undefined risks during the proposed 12 month shelf life, the overall risk was deemed adequate. The risk mitigation strategy was based on the inclusion of the mandatory weekly sterilization program, the documented low bioburden counts in the fluid path, the biofilm removal studies to remove any early formed biofilms should they be present, the inline depyrogenation (KOH, ozone, and filter), and the inclusion of a final 0.2 μm sterilizing filter. While this manufacturing process may not have been deemed a reasonable risk without the high demand associated with the imminent loss of source for current Tc99m generators, this generator was deemed to pose a reasonable risk. Any new information discovered from the post-marketing study or commercial experience will be evaluated as available.

Secondary Reviewer Name and Date (and Secondary Summary, as needed): John Metcalfe, PhD; 02 January 2018

I concur with the primary reviewer's assessment.



John
Metcalf

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Comments: I concur with the primary reviewer's assessment.



Jessica
Chiaruttini

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NDA 202158

**NorthStar Medical Radioisotopes, LLC
5249 Femrite Road
Madison, WI 53718
USA**

**TechneGen Generator System
Sodium Pertechnetate Tc99m Injection, USP**

**Ravindra K. Kasliwal, Ph.D.
Division of Medical Imaging Products**

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Chemistry Review Data Sheet

1. **NDA 202158**
2. REVIEW #: 1
3. REVIEW DATE: 07-Oct-2013
4. REVIEWER: Ravindra K. Kasliwal, Ph.D.
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	04-Jan-2013
Amendment	22-Jan-2013
Amendment	22-Jan-2013
Amendment	23-Jan-2013
Amendment	15-Feb-2013
Amendment	17-Apr-2013
Amendment	10-Jul-2013

7. NAME & ADDRESS OF APPLICANT:

Name: NorthStar Medical Radioisotopes, LLC

Address: 5249 Femrite Drive, Madison WI 53718 USA

Representative: Scott D. Moffatt, Vice President
Regulatory Affairs and Quality

Telephone: 608-230-7163 (office)
608-449-1073 (mobile)

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: TechneGen Generator System
- b) Non-Proprietary Name (USAN): Sodium Pertechnetate Tc99m Injection
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 5
 - Submission Priority: S

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Radiopharmaceutical

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: (b) (4)

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: Rx OTC

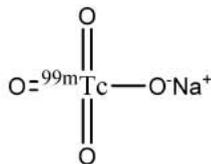
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

- Sodium Pertechnetate Tc 99m



Chemical Formula: NaO₄⁹⁹Tc

Molecular Weight: 185.89

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
26592	V	NorthStar Radioisotopes	TechneGen Generator System	1	Inadequate	30-Sep-2013	Applicant needs to be told that the DMF is deficient.
26426	II	University of Missouri Research Reactor (MURR)	Manufacture of Potassium Molybdate	1	Adequate	18-Sep-2013	No Comments.
(b) (4)				1	Adequate	01-Oct-2013	No Comments

Chemistry Review Data Sheet

(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	27-Feb-1996	No Comments
(b) (4)	III	(b) (4)	(b) (4)	7	N/A	N/A	The DMF is referenced for Bacterial EndoToxin Reduction (BER) Validation Study. This has been reviewed by microbiology.
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	MULTIPLE REVIEWS	The are commonly used stoppers and coatings. These have been reviewed many times.
(b) (4)	V	(b) (4)	(b) (4)	7	N/A	N/A	Sterilization is reviewed by Microbiology. See Micro Review.
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	15-Jul-1998	Reviewed by Richard C. Adams, Ph.D.
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	N/A	No Comments
(b) (4)	III	(b) (4)	(b) (4)	1, 4	Adequate	Microbiology review dated 12-Aug-2013	These vials are commonly used in clinics. The most critical aspect, the sterility aspect, has been reviewed by the microbiology reviewer.

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

IND 109871	NorthStar Medical Radioisotopes, LLC	There have been multiple pre-NDA meetings with the applicant under this IND.
Meeting comments	DARRTS - 14-Oct-2010	Youbang, Liu
Meeting Minutes	DARRTS – 29-Apr-2011	Youbang, Liu
Meeting Comments	DARRTS – 21-Nov-2012	Youbang Liu
Meeting Minutes	DARRTS – 24-Nov-2012	Youbang Liu

Additionally, there have been a number of microbiology reviews microbiology reviews dated 21 October 2010, 02 February 2011, 29 March 2011, 05 April 2011, 13 June 2011, and 11 December 2012.

Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox	Approval	16-Sep-2013	Siham Biade, Pharm.D., Ph.D.
Biopharm	N/A		
LNC	N/A		
Methods Validation	Not recommended	Date of this review	Sodium pertechnetate Tc99m injection is a USP monograph product.
DMEPA			
EA	Categorical exclusion is acceptable	Date of this review	Ravindra K. Kasliwal, Ph.D.
Microbiology	Approvable Pending a Complete Response to Microbiology Deficiencies	30-Sep-2013	Jessica Cole, Ph.D.
CDRH (TechneGen Generator)	CDRH Has comments for Applicant	24-Sep-2013	Prasanna Hariharan, Ph.D.
CDRH (TechneGen Software)	CDRH Has comments for Applicant	24-Sep-2013	Joseph Jorgens, III, Ph.D.

The Chemistry Review for NDA 202158

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is not approvable under section 505 of the FD & C Act from a chemistry, manufacturing and controls perspective. It is recommended as approvable provided CMC, microbiology, CDRH deficiencies are adequately resolved, referenced DMFs are adequate, and associated manufacturing facilities are acceptable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Currently none.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The NDA describes a complex “TechneGen Generator System (TGS)”, which is an automated radionuclide separation system designed for use in a nuclear pharmacy or clinic to separate, purify and provide sterile “Sodium Pertechnetate Tc99m Injection” from externally produced molybdenum-99 (Mo-99). TechneGen consists of three (3) sections. The first is the instrument which houses the various pumps, valves, fluid lines, shielded areas, reagents and control electronics. The second is the computer system which provides a user-interface that gives the user the ability to administer and control the instrument operations. The third is the specially designed container system which houses the Mo-99 solution and is received by the nuclear pharmacy from the production facility on a routine basis.

Potassium Molybdate Mo99 is prepared by neutron bombardment of molybdenum targets that contain molybdenum-98. Mo99 is radioactive and decays, with a half life of 66 hours, to metastable technetium 99m (Tc99m) and technetium Tc99g (ground state). The Potassium Molybdate Mo99 solution in 5M KOH is manufactured and provided to the end user in a specially designed shielded container system. The received potassium molybdate source (Mo-99) is installed (connected) on the TechneGen instrument. The potassium molybdate solution as well as other solutions are moved in TechneGen fluid lines and valves through the aid of syringe pumps that are under computer control. At any given time the Mo-99 solution will also contain Tc99m and Tc99g, based on growth rate since the time of previous separation. Eluting the potassium molybdate Mo99/Tc99m source once every 24 hours will provide an optimal yield of Sodium Pertechnetate Tc99m. However, a potassium molybdate Mo99/Tc99m source solution may be eluted at shorter intervals. Each elution of a Mo99 source essentially removes all Tc99m. (typically $\geq 85\%$ of the available technetium-99m is recovered (entirely in-growth time dependent)). Tc99m begins to accumulate in the Mo99 source solution after each elution as a function of decay of the parent Mo99.

The chemical separation of Technetium-99 from Mo-99 on TechneGen relies on the highly selective resin (ABEC[®] resin) present in a disposable primary separation column. The resin sequesters and retains the pertechnetate anion (i.e., Tc99) while exhibiting virtually no affinity for the molybdate ions, or any other metal ions in solution. This permits an effective means of separation and purification and also simultaneously provides a mechanism to concentrate the Tc99m on the primary resin. The ability to efficiently concentrate the Tc99m renders the TechneGen Generator System capable of utilizing low concentrations of low specific activity Mo99 solutions as source material to produce high specific activity concentrated solutions of Sodium Pertechnetate Tc99m Injection (required by many radiopharmaceutical kits).

Executive Summary Section

To initiate an elution, the source Mo99 solution is passed through the Primary Separation Resin (ABEC®) cartridge, which selectively sequesters and retains the pertechnetate Tc99m anions while passing the Mo99 (and stable molybdenum) into a recovery vessel. After the Mo99 transfer through the primary separation cartridge, it is temporarily retained in a transfer vessel until the Tc99m is eluted from the Primary Separation Cartridge-ABEC resin, then the Mo99 is returned to its original vessel. After allowing sufficient Mo99 decay time for in-growth of Tc99m to occur, it can be recycled through either the same Primary Separation Cartridge for a limited number of times (maximum (b) (4) times) or through a newly installed primary separation cartridge to create another Tc99m elution.

After a rinse of the Primary Separation Cartridge (ABEC) with 5M (b) (4) the pertechnetate containing cartridge is treated with 1.5M sodium acetate (pH 7.0) to neutralize residual hydroxide and provide further decontamination of the Tc99m from the Mo99 source. The sodium pertechnetate Tc99m is eluted from the Primary Separation Cartridge (ABEC) with injectable grade 0.9% sodium chloride solution. The sodium pertechnetate Tc99m eluted from the ABEC cartridge is sequentially passed through the alumina cartridge which is selective (under the elution conditions) for any traces of residual molybdate, that may be present, followed by the sterilization filters. The use of the alumina cartridge is equivalent to a second purification step of the final sodium pertechnetate Tc99m from the parent radioisotope. This alumina cartridge contains activated alumina, similar to that used in all commercial brands of Sodium Pertechnetate Tc99m generators. The final filtered high specific activity concentrated solutions of Sodium Pertechnetate Tc99m Injection is collected in a vial. The Sodium Pertechnetate Tc99m Injection, the packaged solution is assigned a 12 hour expiration dating period.

This final technetium-99m product is intended to meet or exceed the USP specifications for sodium pertechnetate Tc99m injection. Final product Sodium Pertechnetate Tc99m Injection volume is typically (b) (4) mL. The final product is required (package insert) to be visually examined for clarity and particulate material (must be clear, colorless with no evidence of particulate materials), is required to be tested for Molybdenum-99 breakthrough (must be less than 0.15 µCi/mCi of Tc99m at 12 hours post-elution), tested for aluminum (must be less than 10 µg/mL), and tested for pH (must be between 4.5 and 7.5).

B. Description of How the Drug Product is Intended to be Used

The final Sodium Pertechnetate Tc99m Injection product may contain variable range of radioactive concentrations ranging from (b) (4) mCi/mL up to (b) (4) mCi/mL (total (b) (4) mCi / vial ((b) (4) mL)) in 0.9% sodium chloride injection solution. The actual radioactive concentration must be measured at the nuclear pharmacy or clinical site after it has been eluted from the TechneGen Generator.

The Sodium Pertechnetate Tc99m Injection solution can be used similarly as the solution obtained from currently marketed Tc99m generators. Sodium Pertechnetate Tc99m Injection can also be used for preparing various Tc-99m labeled radiopharmaceuticals from the currently marketed "Kits", as they are currently prepared. Hence this Sodium Pertechnetate Tc99m Injection solution can be used interchangeably with the currently available Sodium Pertechnetate Tc99m Injection.

C. Basis for Not-Approval Recommendation

Application is not approval because of inadequate CMC data, inadequate microbiological data, inadequate referenced DMF26592, and manufacturing facilities not ready for inspection (final compliance recommendation is pending).

III. Administrative

A. Reviewer's Signature

Ravindra K. Kasliwal, Ph.D.

B. Endorsement Block – See DARRTS

C. CC Block – See DARRTS

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/s/

RAVINDRA K KASLIWAL
10/07/2013

ELDON E LEUTZINGER
10/07/2013

I fully concur with the primry reviewer's evaluaton, recommendations and conclusions.

DANAE D CHRISTODOULOU
10/07/2013

I concur with the reviewer's conclusions and recommendations.

Product Quality Microbiology Review

30 SEP 2013

NDA: 202-158

Drug Product Name

Proprietary: TechneGen Generator System for Preparation of Sodium Pertechnetate Tc99m Injection

Non-proprietary: Sodium Pertechnetate Tc99m Injection USP

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
04 JAN 2013	04 JAN 2013	07 JAN 2013	11 JAN 2013
22 JAN 2013	22 JAN 2013	N/A	N/A
15 FEB 2013	19 FEB 2013	N/A	N/A
02 APR 2013	02 APR 2013	N/A	N/A
19 APR 2013	19 APR 2013	N/A	N/A
26 APR 2013	26 APR 2013	N/A	N/A
15 MAY 2013	15 MAY 2013	N/A	N/A

Applicant/Sponsor

Name: NorthStar Medical Radioisotopes, LLC

Address: 5249 Femrite Road
Madison, WI 53718

Representative: Scott Moffatt

Telephone: 608-230-7163

Name of Reviewer: Jessica G. Cole, PhD

Conclusion: Recommended as Approvable Pending a Complete Response to Microbiology Deficiencies

Product Quality Microbiology Data Sheet

- A.
- 1. TYPE OF SUBMISSION:** New 505(b)(2) NDA
 - 2. SUBMISSION PROVIDES FOR:** New Tc99m generator system for installation and use in radiopharmacies.
 - 3. MANUFACTURING SITE:** Multiple manufacturing sites are utilized for the components. See Section P.3.1 for the sites relevant to microbiology. NorthStar will release the generator and kits from the following site:

NorthStar Medical Radioisotopes, LLC
5249 Femrite Road
Madison, WI 53718
 - 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
 - Sterile solution for intravenous injection or oral administration
 - (b) (4)
 - Non-preserved solution in a 20 mL glass vial with rubber stopper
 - The patient dosage form is manufactured in a non-sterile generator system installed in a radiopharmacy
 - 5. METHOD(S) OF STERILIZATION:** Sterile filtration
 - 6. PHARMACOLOGICAL CATEGORY:** Multiple organ imaging indications. This product is proposed for use with a variety of reagent kits.
- B. **SUPPORTING/RELATED DOCUMENTS:** There have been multiple pre-NDA meetings with the applicant. For more information see the IND 109,871 microbiology reviews dated 21 October 2010, 02 February 2011, 29 March 2011, 05 April 2011, 13 June 2011, and 11 December 2012.

There were two official meeting packages reviewed during the PDUFA cycle. The May meeting dealt specifically with product quality microbiology issues associated with this application and the July meeting focused on the proposed user guides and human factors test protocol. See DARRTS for the microbiology reviews dated 24 May 2013 and 29 July 2013 for more information. There were multiple official teleconferences held with the applicant during the review cycle and the minutes from those meetings can be found in DARRTS.

(b) (4) describes the manufacture of the 20 mL sterile empty vials for use with the collection kit. The microbiology review dated 12 August 2013 found the

DMF adequate for manufacture of [REDACTED] (b) (4). This review was submitted to BIRAMS on 12 August 2013.

- C. REMARKS:** This submission is electronic and is nominally in the CTD format. The original NDA submission on 04 January 2013 did not contain microbiology data and was not reviewed in support of this application but has been left in the table on page 1 to provide the submission and assignment dates. The reference product is Mallinckrodt Medical's NDA 17-243 approved on 23 November 1973. This submission supports a White House initiative to decrease the use of high-enriched uranium products.

The following information request was sent to the applicant on 12 February 2013 and a response was received on 19 February 2013. The response was found to be not applicable due to the use of sterilizing filters during the studies. No further information is provided in this review. For more information, see the 24 May 2013 meeting review.

Provide the name and location of the study report for protocol 75T01866. We note that the protocol states the following in section 10.0 Reporting Results: "A final report will be completed. The report will contain at a minimum a summary of methods, test materials, results, completed protocol attachments, deviations which occurred and their resolution, and conclusions. Circumstances, which may have affected the quality or integrity of the data, will be described. The final report will be signed and dated by the Study Director and approved by the QA Department Head."

The following information request was sent to the applicant in the filing communication on 18 March 2013 and a partial response was received in the 02 April 2013 meeting request. Additional information was provided in the 19 April 2013 amendment. An updated response was provided in the 26 April 2013 amendment. The responses have been incorporated into the relevant sections of this review and the 24 May 2013 meeting package review, as applicable.

Microbiology Comment:

Please provide the following information or a reference to its location in the relevant submission.

1. The studies submitted in support of the microbiological control of the TechneGen system are not adequate to demonstrate control of the system. We recommend that you design a new study and suggest you use the cleaning protocol validation studies as a starting point. We encourage you to challenge your system to evaluate the worst case situation. We are available to discuss a revised protocol. The following deficiencies from the submitted studies are being provided to assist you in the design of a new study.

a. Samples used to evaluate the routine bioburden of the system were collected after sterile filtration and provide no useful information to the Agency. Section 2.0 of Protocol 75T01862 rev 02 states this protocol was executed "to determine the levels of microbial contamination resident in the fluid path of the TechneGen (Instrument system) following an extended period of intermittent use when in an unclassified laboratory environment." However, the test procedure instructs users to collect a sample after passing it through dual 0.22 µm filters. (See Sections 6.4 and 6.5) We note that the IND meeting package submitted 08 March 2011 and the NDA contain a Microbiology Master Validation plan (75T01858 revisions G and 01, respectively) that describe sampling prior to the sterilizing filter.

b. The decision to run the cleaning protocol immediately prior to collecting samples for protocols 75T01862 and 75T01866 does not allow the Agency to evaluate the worst case situation. More relevant information would be gathered from an elution collected immediately prior to a scheduled cleaning protocol. A comparison of the bioburden prior to and immediately following a cleaning protocol would also provide useful information.

c. We are concerned with the interpretation of microbiological data in the submitted studies. Specifically (b) (4) recovered 1 CFU/mL in several samples from Protocol 75T01866 yet NorthStar reported <1 CFU/mL in Table 7 from Module 3.2.P.3.3. We note the reference to a 9 mL sample but (b) (4) records submitted on 19 February 2013 indicate that only 1 mL of this 9 mL sample was plated.

d. The cleaning validation studies did not include a positive control that confirmed organisms were still viable at the time of the sampling. It is not clear to the Agency whether the low numbers of organisms recovered was due to the cleaning procedure or decreased viability of *Bacillus atrophaeus* in sodium acetate over the study duration.

2. Confirm that the (b) (4) and (b) (4) 0.22 µm sterilizing filters are both proposed for commercial use.

3. 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.

4. Explain why the (b) (4) 0.22 µm filter was not used during the media fills. We refer to 75T01863 Section 6.1.

5. Explain why the sodium acetate and sterile collection vials used for media fills are different from those proposed for production. Explain how these components differ and justify their use.

6. Provide the (b) (4) sterilization validation studies for the (b) (4) Spike with 0.22 µm sterilizing filter. Your inclusion of a copy of the label is not sufficient. Alternately, provide a letter of authorization to a DMF reference to a 510k that contains this information. The letter of authorization should clearly indicate where in the DMF the information is located.

7. Provide the microbial retention studies in support of the (b) (4) Spike with 0.22 µm sterilizing filter. We note the inclusion of Technical Report #1994-03-08 but this study has insufficient detail with which to assess the microbial retention results presented. For more information, please refer to the 2004 Aseptic Processing Guidance and PDA TR 26. We suggest you model the studies after those conducted to support the (b) (4) 0.22 µm filters. We note the claim that this filter is a secondary filter and the primary sterilizing filter is intended to be the proposed (b) (4) filters. As this spike filter is downstream of the (b) (4) filter and provides the last product contact point before the collection vial the microbial retention studies are required. However, you may submit a justification for not demonstrating the capacity to retain 10⁷ CFU/cm² (as is traditionally required).

8. Provide the sterilization validation studies and microbial retention studies for the (b) (4) filter unit (77C01242). Alternately, provide a letter of authorization to a DMF that contains this information. The letter of authorization should clearly indicate where in the DMF the information is located.

9. Describe how the inlet pressure for (b) (4) filter unit (77C01242) is controlled/measured by the system to insure the filter is not exposed to pressure >75 bar.

10. Indicate which kit contains (b) (4) filter (77C01242) and indicate how long this filter is used before being replaced.

11. Provide a description of vented spike 77C01925 used in the cleaning validation studies and explain how it differs from the vented spike 77C01891 planned for production. Indicate whether spike 77C01925 contains the same in-line 0.22 µm filter as 77C01891. We refer to your submission made on 19 February 2013.

12. If the vented spike in question 11 above contains a 0.22 µm filter provide a justification for collecting sample after passage through a sterilizing filter. For more information we refer you to question 1.

13. Protocol 75T01858 Table 1 appears to have a typo as the sterilizing filter and vent filter are listed with the same part number. Please clarify.

14. Submit the final summary report from Protocol 75T01997. We note that the protocol was submitted to Module 3.2.P.3.5 but was labeled as the report.

15. Clarify how the (b) (4) mL and (b) (4) mL hydrogen peroxide solutions are manufactured. Module 3.2.P.3.4 Figure 8 describes the manufacturing process and the flow indicates that the solution is (b) (4) capped, and then release tested and labeled. This appears to be an error as you indicate that vials are (b) (4) prior to (b) (4) capping.

16. Confirm that the 3% hydrogen peroxide lots presented in JN11I0658 were (b) (4) sterilized for (b) (4) prior to inclusion on stability. This reviewer understands that hydrogen peroxide is not (b) (4).
17. Provide the specifications (with test methods) for the (b) (4), sodium acetate, and hydrogen peroxide made by North Star (PSI).
18. Provide the supplier, sterilization method, and sterilization validation studies for the (b) (4) wipes.

General comment: Please do not submit files in duplicate to different parts of the NDA. It is very confusing to review and is not an efficient use of resources for the Agency as both sets of files have to be confirmed to be identical. We note that the 19 February 2013 submission contained identical files submitted to Module 3.2.P.3.3 and Module 3.2.P.3.5.

The following comments were sent to the applicant prior to the May 2013 meeting. No response was required from the applicant.

Microbiology Comment

The following comments are being provided to help focus the discussion for the Type C meeting.

As was stated in the Filing communication, the studies submitted in NDA 202-158 do not support the microbiological control of the TechneGen system. We refer you to comment 1 in the filing communication and the specific, detailed reasons why these studies are not adequate (1a-1d). These comments were provided to help you understand what additional information is needed and we encourage you to consider those comments when evaluating your studies.

Concerning the design of a new study, it is your responsibility to document that the proposed commercial product is adequate for its intended use. In the 02 April 2013 meeting request, NorthStar stated that records were being evaluated to determine whether documentation supports NorthStar's claim that samples were collected pre-filtration and not post-filtration (as is stated in the NDA document 75T01862 rev 02). NorthStar also stated that the bioburden and cleaning studies may be redesigned and repeated (data to be submitted 31 May 2013). If the comments in the filing communication can be addressed with the above changes, then there is no reason to design a new study. However, if NorthStar decides that new studies are required to address the deficiencies, the Agency is willing to provide feedback on a revised protocol. The Agency will not design a study for NorthStar but will answer specific questions pertaining to the previously identified deficiencies or review a proposed protocol submitted in advance of the Type C meeting.

We note your reference to the Microbiology Master Test Plan 75T01858 in Question 1. This test plan is a summary of proposed microbiology studies. The Agency found significant inconsistencies between the Master Test Plan and the referenced test protocols. We listed these deficiencies in the Filing communication and once again encourage you to review the information previously provided. As NorthStar technicians were trained on the relevant protocols, this reviewer used the information found in protocols and reports in lieu of information found in 75T01858.

The 02 April 2013 submission requested clarification from the Agency in Comment 1 subpart c. The referenced information may be found in Sequence 0005 submitted on 19 February 2013 Module 3.2.P.3.3 Reports 1, 2, and 3.

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Executive Summary

I. Recommendations

- A. Recommendation on Approvability** - Recommended as Approvable Pending a Complete Response to Microbiology Deficiencies.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – Not applicable.

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – This is a complex, non-sterile manufacturing system that uses sterile reagent solutions and some sterile components to produce an injectable radiopharmaceutical. The user is required to complete multiple aseptic connections before production of the patient dosage form. The generator will be located in radiopharmacies across the United States and the tubing will be cleaned once a week with 3% hydrogen peroxide.
- B. Brief Description of Microbiology Deficiencies** – The routine bioburden and cleaning protocol for the manufacturing system has not been evaluated. The sterilization validation information is not adequate to demonstrate sterility of the reagent solutions and components. There is no information to support the use of the non-sterile drug product tubing for 12 months or the device for (b) (4) [REDACTED]. The labeling has not been finalized and cannot be assessed at this time.
- C. Assessment of Risk Due to Microbiology Deficiencies** – This product has a high risk of producing a final drug product that is not sterile.
- D. Contains Potential Precedent Decision(s)**- **Yes** **No**
Approval of this application could create a precedent but at this time, no precedent setting decisions have been made.

III. Administrative

- A. Reviewer's Signature** _____
Jessica G. Cole, PhD
Microbiology Reviewer

B. Endorsement Block

John Metcalfe, PhD
Senior Microbiology Reviewer

C. CC Block

In DARRTS

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/s/

JESSICA COLE
09/30/2013

JOHN W METCALFE
09/30/2013
I concur.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 29 July 2013

TO: Alberta Davis-Warren
Regulatory Health Project Manager
CDER/OND/DMIP

FROM: Jessica G. Cole, PhD
Review Microbiologist
CDER/OPS/New Drug Microbiology Staff
(301) 796-5148

THROUGH: John Metcalfe, PhD
Senior Microbiology Reviewer
CDER/OPS/New Drug Microbiology Staff

SUBJECT: NDA: 202-158
Submission Date: 15 May 2013
Drug Product: TechneGen Generator System
Applicant: NorthStar Medical Radioisotopes, LLC

A product quality microbiology review of the Type C meeting package for NDA 202-158 submitted on 15 May 2013 is complete. This is the second meeting package review to occur during the PDUFA review cycle. The microbiology review of meeting package #1 is dated 24 May 2013. The 15 May 2013 meeting package contains a human factor study protocol and three revised user manuals. There were three questions submitted in this meeting package and Question 1 and 3 required a product quality microbiology response. The questions are reproduced below in bold and the microbiology response follows in normal type. A summary of the meeting minutes may be found in DARRTS.

1. NorthStar has reviewed the comments associated with the submitted Operators Manual for “lack of user friendliness” and has made substantial changes not only to the content but to the organizational structure of the manual. The operator’s manual has been re-organized into three Guides as follows:

- a. TechneGen Generator System Operators Guide ([94S01916](#))
- b. TechneGen Generator System Controller Applications Guide ([94S03230](#))
- c. TechneGen Generator System Accessory Kits and Mo99 Source Assembly Guide ([94S03231](#))

With the re-organization of the manual structure and the improvements and standardization of the terms and processes within the guides does the Agency think that

MEMORANDUM

NorthStar has improved the clarity and user friendliness of the TechneGen Generator instruction materials to a satisfactory level?

We agree that the revised guides are an improvement. The meeting package refers to a generation 2 system and the supplied guides are for the generation 1 system. Both generation 1 and generation 2 systems are proposed for use in the human factors studies. As the generator system has not been finalized, the user guides are considered preliminary. A complete review of the final proposed product and associated user guides will be conducted once product development is complete. The following comments are being provided to aid you with the continued development of the user guides.

1. The guides should not refer to (b) (4) or (b) (4) as these references are not applicable. (b) (4) and USP<797> applies to pharmacy compounding. You should remove all references from your proposed labels and from all three guides.
2. The guides should require ISO 5 and ISO 8 environments. It may be useful to provide a description/example of these environments.
3. The sterilizing filter should be integrity tested after use. A description of acceptable methods and acceptance criteria may be useful to the user.
4. The Aseptic Technique (part 8) of the Operators Guide should be moved up in the manual. It should appear before NorthStar's contact information.
5. The Aseptic Technique (part 8) of the Operators Guide should provide additional information on aseptic manipulations. The information that NorthStar was referencing in (b) (4) should be included in this section to provide the user all needed information to safely operate the generator. The instructions should be appropriate for the intended use and appropriate for the intended user. When revising this section please consider the training and experience level of the user. If routine radio pharmacy practices do not include full gowning then this section should be revised to reflect routine/minimum acceptable practices.
6. The controller application guide states on page 16 that the lines are (b) (4). The lines are (b) (4) and should not be referred to as such.
7. The Accessory Kit and Assembly Guide refer to a (b) (4). This should be changed to an ISO 5 environment.

3. NorthStar has provided a Training Syllabus (90Q03232) as part of the Human Factors Protocols, (75T03226) that will be used to train authorized users at customer sites. NorthStar intends to improve this syllabus as training experience is gained. Does the agency agree that NorthStar has designed a training syllabus that includes the essential areas of training that will enable TechneGen Generator Users to successfully operate the equipment?

Insufficient information has been provided on the training syllabus and training certification program. Additional details, including the proposed training CD (multimedia presentation) and quick guides, should be submitted to the Agency.

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/s/

JESSICA COLE
07/29/2013

JOHN W METCALFE
07/29/2013
I concur.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 24 May 2013

TO: Alberta Davis-Warren
Regulatory Health Project Manager
CDER/OND/DMIP

FROM: Jessica G. Cole, PhD
Review Microbiologist
CDER/OPS/New Drug Microbiology Staff
(301) 796-5148

THROUGH: John Metcalfe, PhD
Senior Microbiology Reviewer
CDER/OPS/New Drug Microbiology Staff

SUBJECT: NDA: 202-158
Submission Date: 26 April 2013, Type C Meeting Package
Drug Product: TechnGen Generator System (Sodium Pertechnetate Tc99m)
Applicant: NorthStar Medical Radioisotopes, LLC

A product quality microbiology review of the meeting package for NDA 202-158 is complete. NorthStar requested this meeting after receipt of the Microbiology comments in the 74-day filing communication. There were four product quality microbiology questions in the briefing package. Those questions are reproduced below in bold and the microbiology response follows in normal type. A teleconference to discuss the microbiology responses occurred on 22 May 2013. A summary of the discussion with the applicant may be found in the meeting minutes in DARRTS. Briefly, the applicant agreed to revise the protocols or provided an appropriate remediation to address the comments below. The bioburden and cleaning studies will be repeated and the applicant's goal is to submit the results from those studies by the end of July 2013.

Question a.

Items 1a & 1b: A "Redlined" revision of the Cleaning & Sanitization Validation protocol (75T01866 Rev 02A) & Bioburden/Hold time Study (75T01862 Rev 02A) are provided with updates to include a pre-filtration bioburden sample prior to the instrument cleaning process. These procedures (75T01866 & 75T01862) have been revised to include a pre-cleaning, pre-filtration bioburden sample in addition to the post cleaning bioburden sample. Provided that NorthStar is able to obtain successful results, does the Agency concur that the revised protocols

MEMORANDUM

provide a worst-case scenario for microbiology control with respect to operation of the TechneGen Generator System?

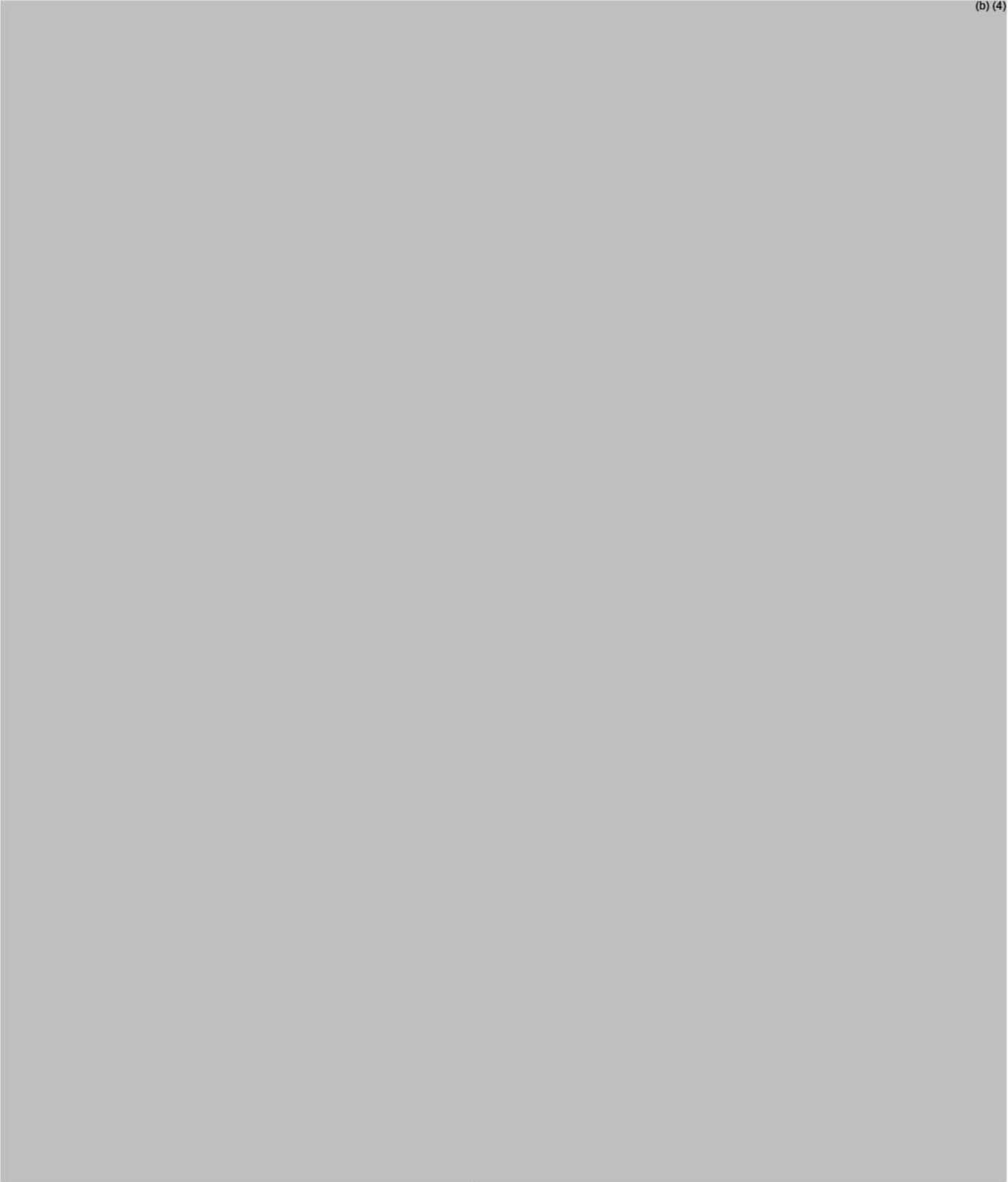
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/s/

JESSICA COLE
05/24/2013

JOHN W METCALFE
05/24/2013
I concur.