CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202158Orig1s000

OTHER REVIEW(S)

OFFICE OF DEVICE EVALUATION
DIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL,
RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES

GENERAL HOSPITAL DEVICES BRANCH
INTERCENTER CONSULT MEMORANDUM

Date	January 16, 2018
To	Alberta E Davis-Warren Alberta.Davis-Warren@fda.hhs.gov OMPT/CDER/OND/ODEIV/DMIP 301-796-3908
Requesting Division	Division of Medical Imaging Products (DMIP)
From	Robert Meyer, Mechanical Engineer / John McMichael, Biomedical Engineer CDRH/ODE/DAGRID/GHDB
Through (Team Lead)	John McMichael, ICC Team Lead CDRH/ODE/DAGRID/GHDB
Through (Branch Chief)	CAPT Alan Stevens CDRH/ODE/DAGRRID/GHDB
Subject	Consult for Submission # NDA 202158 ICCR2017-00926 ICC# ICC1700405 and ICC1700052
Recommendation	**Device Constituent Parts of the Combination Product are Approvable with the following recommended Post-Market Requirement:** **During the annual maintenance check of each one of your systems:** **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 by the software.** **4. Report any elution volumes which are out of tolerance.** **This information is required to ensure that the long-term durability of the system is acceptable and the performance of the system does not degrade with time.**

Digital Signature Concurrence Table	
Reviewer	John C. Mcmichael -S
Team Lead	2018.01.17 16:30:32 -05'00'
Branch Chief	Alan M. Stevens -S Digitally signed by Alan M. Stevens -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300189211, cn=Alan M. Stevens -S Date: 2018.01.18 07:35:14 -05'00'

1. Submission Overview

Table 1. Submission Information	
ICCR # (Lead)	ICCR 2017-00926
ICCR SharePoint Link	http://sharepoint.fda.gov/orgs/OSMP/ocp/ICRR/Lists/ICRR%20Forms/DispForm.aspx?ID=1111
ICC tracking # (Lead)	ICC-1700405 and ICC-1700052
Submission Number	NDA 202158
Sponsor	NorthStar
Drug/Biologic	Sodium Pertechnetate Tc 99m
Indications for Use	Sodium Pertechnetate Tc99m Injection produced by a TechneGen Generator System is a diagnostic radiopharmaceutical agent intended for use in children and adults for the following indications: ☐ Brain Imaging (including cerebral radionuclide angiography) ☐ Thyroid Imaging ☐ Salivary Gland Imaging ☐ Placenta Localization ☐ Blood Pool Imaging (including radionuclide angiography) ☐ Urinary Bladder Imaging (direct isotopic cystography) for detection of vesico-ureteral reflux In addition, it is indicated for use in adults for Nasolacrimal Drainage System Imaging (dacryoscintigraphy). Sodium Pertechnetate Tc99m Injection is also used to reconstitute a variety of reagent kits, commonly referred to as Technetium Tc99m Kits, and with each reconstituted kit used for specified diagnostic imaging indications.
Device Constituent	RadioGenix System
Related Files	N/A

Table 2. Review Team	
CDER Lead Review Division	CDER/DMIP
Submission RPM	Alberta E Davis-Warren and Thao Vu
Lead Device Reviewer	Robert Meyer
The CDRH review is being managed under ICC #: ICC1700405	
Below is a list of the Discipline Specific ICCR#, ICC# and CON#. The CON# are under ICC1700405 in CTS.	

Discipline Specific Consults	Reviewer Name (Center/Office/Division/Branch)	ICCR #	ICC #	CON #
Software	Joseph Jorgens	2017-00926	ICC1700405 / ICC1700052	CON1712072 / CON174438
EMC	Donald Witters	2017-00926	ICC1700405/ ICC1700052	CON1712070 / CON174442
Electrical Safety	Michael Long	2017-00926	ICC1700405/ ICC1700052	CON1712069 / CON174440

Mechanical Eng.	Prasanna Hariharan	2017-00926	ICC1700405 / ICC1700052	CON1727231 / CON174439
Human Factors	Shannon Hoste	2017-00926	ICC1700405	CON1712185
Biocompatibility*	Sarah Mollo	2017-00926	ICC1700405 / ICC1700052	CON1712067 / CON174437

*Consult cancelled after informal discussion with Dr. Mollo and CDER revealed no need for consult

Table 3. Important Dates	
Final Lead Device Review Memo Due	1/17/18

TABLE OF CONTENTS

2. PURPOSE/BACKGROUND

2.1. Scope

CDER requests review of the RadioGenix elution system, and the associated DMF (DMF 26592). This review is requested through two ICCs. ICC 1700405 was sent by Ms. Davis-Warren for review of the system and its entirety, and ICC1700052 was sent by Thao Vu for the system DMF; both ICC's are covered in this review memo.

2.2. Indications for Use

Combination Product	Indications for Use
Sodium Pertechnetate Tc99m	Sodium Pertechnetate Tc99m Injection produced by a TechneGen Generator System is a diagnostic radiopharmaceutical agent intended for use in children and adults for the following indications: – Brain Imaging (including cerebral radionuclide angiography) – Thyroid Imaging – Salivary Gland Imaging – Placenta Localization – Blood Pool Imaging (including radionuclide angiography) – Urinary Bladder Imaging (direct isotopic cystography) for detection of vesico-ureteral reflux In addition, it is indicated for use in adults for Nasolacrimal Drainage System Imaging (dacryoscintigraphy). Sodium Pertechnetate Tc99m Injection is also used to reconstitute a variety of reagent kits, commonly referred to as Technetium Tc99m Kits, and with each reconstituted kit used for specified diagnostic imaging indications.
Device if previously cleared/approved	N/A

3. ADMINISTRATIVE

3.1. Documents Reviewed

Document Title	Location
a1-facilities-and-equipment - Copy.pdf	GSR 026592 (DMF)/seq.0001/m3
Response to Information Request dated Nov. 01, 2017.pdf	GSR 026592 (DMF)/seq.0011/1.11

4. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

Drug Product Description:
[From: GSR NDA 202158 – 0000 m3 - description-and-composition.pdf]
Sodium pertechnetate Tc99m is an inorganic compound with the formula Na99mTcO4. This colorless salt consists of the cation Na+ and anion 99mTcO4−. It is versatile and important radiopharmaceutical for diagnostic use. The advantages to Tc99m include its wide-spread availability (via a Mo99/Tc99m generator system), **its short half-life of 6 hours and the low radiation exposure to the patient**, which allow a patient to be injected with diagnostic amounts of radioactivity that produce high quality and detailed images of various body systems and functions. The chemistry of Sodium Pertechnetate Tc99m makes it easy to label a number of different ligands which have different physiological characteristics. This makes it possible to image the structure and function or a variety of organs in different parts of the body.

Sodium Pertechnetate Tc99m Injection may contain variable range of radioactive concentrations ranging from less than 1 mCi/mL up to greater than 1000 mCi/mL. **The actual radioactive concentration must be measured at the nuclear pharmacy or clinical site after it has been eluted from a commercial generator or extracted from the NorthStar Generator System.** A representative or typical qualitative and quantitative composition statement is provided in Table 1. The quality and purity of the Sodium Pertechnetate Tc99m Injection meets all requirements specified in the current revision of the USP monograph for this item.

Table 1 Qualitative and Quantitative Composition of Sodium Pertechnetate Tc99m Injection* (Derived from TechneGen Generator System)

(b) (4)

Final Container/Closure:
The Sodium Pertechnetate Tc99m is dispensed into 20 mL vials. The glass is USP Type I. The stoppers are supplied by (b) (4) formulation. The stoppers are secured in place with (b) (4). NorthStar provides 0.9% sodium chloride injection for use to operate the TechneGen Generator System. In addition to 0.9% sodium chloride injection, the following processing reagents are provided for use with the TechneGen Generator System: 3% hydrogen peroxide, (b) (4) and 1.5M sodium acetate. All processing reagents are sterile and non-pyrogenic.

System Description:
The following is extracted from document "a1-facilities-and-equipment.pdf":

General description (page 6)
The RadioGenix instrument is the component of the RadioGenix System (RGX) used to produce Tc-99m for use as a sodium pertechnetate, Tc-99m imaging agent and for preparation of a number of Tc-99m labeled radiopharmaceutical agents used in diagnostic imaging procedures. The RGX processes Mo-99 that is produced via nuclear reaction and separates and concentrates the decay product sodium pertechnetate, Tc-99m. The eluate is suitable for preparing USP Sodium Pertechnetate Tc 99m Injection as a drug or its use in preparing various diagnostic imaging agents from radiopharmaceutical Tc-99m reagent kits.
The RadioGenix System is a dedicated instrument for use by a radioactive material (RAM) authorized practitioner and/or trained nuclear pharmacist operating under the local state Practice of Pharmacy or equivalent regulations.

The RadioGenix Instrument
The RadioGenix System consists of three (3) major physical components:

- The first component is the host computer running the custom application software.
  - The host computer manages the application software, which provides the administrative controls to set up the instrument, define users and permissions, operate the instrument, and enter information about elutions. There is one assigned Administrator. The software application also validates each Tc-99m elution protocol execution for appropriate protocol identity, proper instrument communications, instrument status and messaging, and issues prompts pertaining to the protocol operations. The application screen provides the capability for a user to monitor commands and execution of commands occurring on the instrument during the Tc-99m elution process

- The second is the instrument itself which houses an assortment of pumps, valves, fluid lines, radiation shielding, sensors, indicators and control electronics. Consumables for the system are the source vessels, discarded materials containers, chemistry reagents and separation cartridges that are utilized during the required sequences and methods for isotopic separation. All components are vended from qualified suppliers.

- The third component is the cabinet, which houses the discarded material containers, the source and transfer vessels, the computer, and a battery backup system (UPS). The system also includes all of the shielding necessary to keep the cumulative radiation dose to acceptable levels during in-growth and isotopic separation procedures.

[Page 8] The RadioGenix instrument has the ability to run unaided by the host computer. It has an integrated **radiation detector that permits monitoring movement of radioactivity** during the elution process and a pressure sensor that detects over and under pressure conditions as well as **performing a test of filter integrity**.

Product Requirements
The Radiogenix automated synthesis module produces Sodium Pertechnetate Tc99m Injection in proportion to the quantity of Mo99 that is applied to the primary separation cartridge. Over the life of the Mo99 source, each elution will contain an amount of technetium Tc99m in direct proportion to the quantity of Tc99m present in the potassium molybdate Mo99 solution transferred through the separation cartridge. This quantity will vary with the initial strength (mCi) present in the source, the decay time, and the elapsed time since the previous separation (Tc99m extraction).

The Radiogenix Operator is responsible for assaying the quantity of radioactive Sodium Pertechnetate Tc99m Injection in each elution using a suitably calibrated radiation detection system. A dose calibrator is commonly used for this measurement. Each elution must be tested for the presence of residual Mo99 in the solution using a suitably calibrated detection system that is capable of distinguishing the high energy gamma emissions from the Mo99 from the lower energy emissions of the Tc99m. The quantity of Mo99 must not exceed a ratio of 0.15 µCi of Mo99 per mCi of Tc99m at the time it is administered to a patient.

From the Label:

Requirement	Requirement Description	Specification	Test Protocol
			(b) (4)

Radiogenix Requirements review – [from a1-facilities-and-equipment.pdf page 212]:

2 RGX System General Requirements

2 Requirement	Ver.	Val.
(b) (4)		

3 Product – Tc-99m

3 Requirement	Ver.	Val.
(b) (4)		

4 System Waste

4 Requirement	Ver.	Val.
(b) (4)		

NorthStar MEDICAL RADIOISOTOPES, LLC	Functional Customer Requirements RadioGenix	Number: 91S03218 Rev: 07 Page 6 of 23

4 Requirement	Ver.	Val.
(b) (4)		

6 Chemistry and Microbiology

6 Requirement	Ver.	Val.
(b) (4)		

6 Requirement	Ver.	Val.
(b) (4)		

7 (b) (4)

7 Requirement	Ver.	Val.
(b) (4)		

5. DESIGN CONTROL REVIEW

5.1. Design Review Summary

The RadioGenix System is an automated radionuclide separation system designed for use in a nuclear pharmacy or clinic to separate, purify and sterilize sodium pertechnetate Tc- 99m injection from externally produced Mo-99. The system is an arrangement of purchased parts all vended from certified manufacturers. Radiogenix only designs the arrangement of components, other than the product vial shield component.

The Sponsor adequately verified the system repeatability and reliability through functional verification techniques and through software verification techniques. The functional verification includes analyses of the final elution solution quality and volume. In addition the Sponsor evaluated the volume and pressures associated with the three reagents used to create the final elution solution and flush the system between elutions.

In addition to verifying the essential fluid volumes for each elution the Sponsor evaluated the fluid lines, and connections to ensure they function as intended. The fluid lines are assessed for leakage and pressure. The system software and pressure sensor is verified to detect if the pressure within the lines is out of specification. The fluid line verification documentation was reviewed by the Lead Reviewer and the Mechanical Engineering consult, and deemed acceptable, yet a post market commitment is requested to verify the durability of the PEEK lines.

The system uses [redacted] (b) (4) to sterilize the fluids lines on a periodic schedule. The components functionality is verified to function per software controls adequately. The sterility of the lines is reviewed by a microbiologist in CDER, and in summary deemed acceptable.

The software controls and development was reviewed by a Joseph Jorgens III in CDRH/OSEL, and is considered adequate.

The EMC of the system was reviewed by Donald Witters in CDRH/OSEL and is considered adequate.

The electrical safety of the system was reviewed by Michael Long in CDRH/OSEL and is considered adequate.

5.1.1. Design Control Documentation Check

Design Control Requirement*	Signed/Dated Document Present		Submission Location
	Yes	No	
Design Requirements Specifications included in the NDA / BLA by the Combination Product Developer	X		a1-facilities-and-equipment.pdf – GSR026592/m3
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.	X		a1-facilities-and-equipment.pdf – GSR026592/m3
Risk Analysis supplied in the NDA / BLA by the Combination Product Developer	X		a1-facilities-and-equipment.pdf – GSR026592/m3
Validation Data • Human factors • Clinical data	X		a1-facilities-and-equipment.pdf – GSR026592/m3
		X	
Traceability Documentation	X		a1-facilities-and-equipment.pdf – GSR026592/m3

6. DESIGN VERIFICATION AND VALIDATION REVIEW

6.1. Summary of Design V&V Attributes

Design Verification / Validation Attributes	Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing	X		
To-be-marketed device was used in the pivotal clinical trial			X
Verification methods relevant to specific use conditions as described in design documents and labeling	X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)	X		
Traceability demonstrated for specifications to performance data	X		

Discipline -Specific Design Verification / Validation adequately addressed*						
	Consult needed			Consultant	Attributes Acceptable	
	Yes	No	N/A		Yes	No
Engineering (Materials, Mechanical, General)	X			Prasanna Hariharan	X	
Biocompatibility			X			
Sterility			X			

Software / Cybersecurity	X			Joseph Jorgens	X	
Electrical Safety / EMC	X			Michael Long/ Donald Witters	X	
Human Factors	X			Shannon Hoste	X	

6.2. Design Validation Review

Design Validation Attributes	Yes	No	N/A
Phase I/II/III Study utilized the to-be-marketed device		X	
Bioequivalence Study utilized to-be-marketed device		X	
Simulated Actual Use Study utilized to-be-marketed device	X		

Design validation is completed through a human factors study that involved applicable users. The Human Factors report is reviewed by Dr. Shannon Hoste. In addition, validation is considered by DMEPA and the radioactive clinical team within CDER, and considered acceptable.

6.3. Design Verification Review

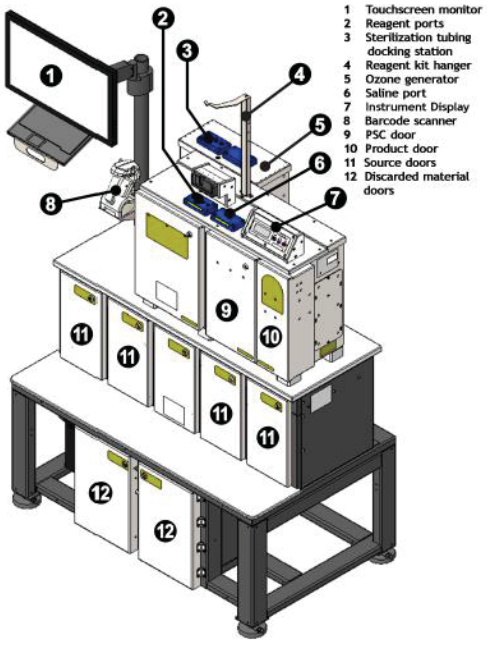
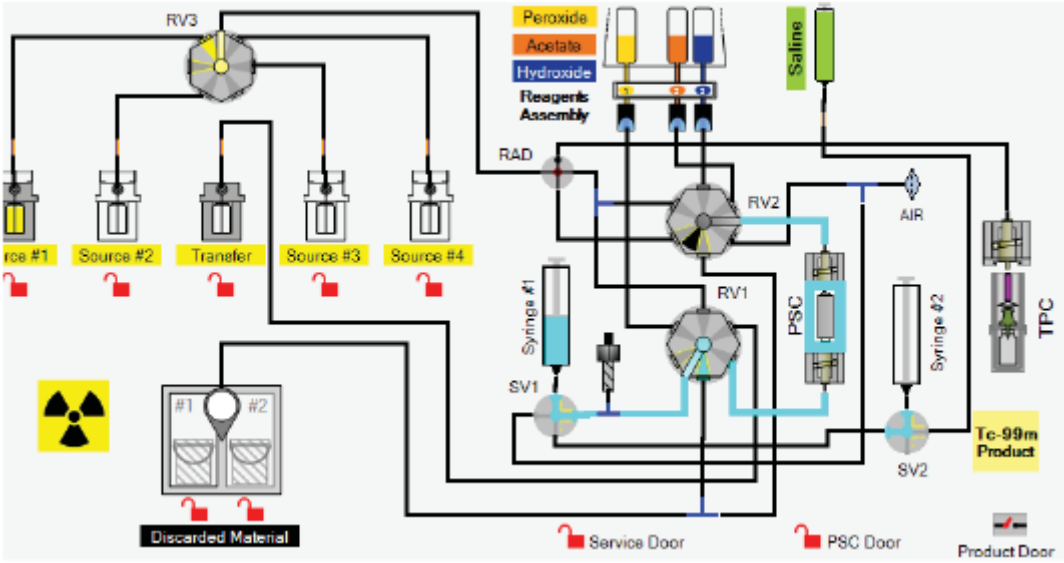


Figure 4. RGX System Overview (Computer CPU and UPS are located on at the bottom left of the cabinet)

(b) (4)



Design verification documentation is located in DMF 026592 document "a1-facilities-and-equipment - Copy.pdf".

Radiogenix Reliability and Repeatability

The Sponsor describes testing completed to demonstrate "robustness" or reliability and repeatability on page 54 of document "a1-facilities-and-equipment - Copy.pdf". The robustness test protocol begins on page 1176 and the report begins on page 1216.

System Repeatability

System repeatability was structured to test unit repeatability, and system to system repeatability using three separate RGX systems and the three reagents used to process the Tc-99 elution (KOH, NaAc, H2O2). The Sponsor notes "The concluding run of repeatability analysis slightly exceeded the upper (b) (4) volume value. As such, the Upper Specification Limit (USL) for volume was modified to a new value, as was documented in Protocol Exception Number RGXRPT004. With the adjustments, the repeatability analysis demonstrated results which were deemed acceptable and allowed the testing to proceed to the specification limit testing section." In summary the Sponsor states the three systems were able to deliver each reagent within specifications.

Specifications Limits Testing

In addition to functional testing to demonstrate repeatability the Sponsor completed a Taguchi limits test statistical analysis; " Using Minitab, a Taguchi 12 factor test was created using a T32 test configuration." The Sponsor states "the matrix of Upper and Lower Specification Limits were tested to limits beyond the repeatability values (a Cpk value > (b) (4)) which demonstrates the systems functions at levels beyond expected operating conditions with a high level of confidence and reliability. A set of secondary tests performed consisted of fluid transfer, partial filled PSC and TPC, and Upper and Lower limits of Reagents."

In conclusion the Sponsor states that when the system is functioning and specification limits it is able to [redacted] (b) (4) loss still results in enough product available for patient use and is considered acceptable for the product application."

Safety Margin Test Procedure and Report (page 1174, and 1215 of a1-facilities-and-equipment - Copy.pdf).

The Sponsor states the objective of this test is to "Determine the robustness of the RGX Elution process as a measure of its capacity to remain unaffected by deliberate variations in processing parameters and provides an indication of its reliability during normal usage. The objective of this robustness testing is to develop test cases which determine the RGX system repeatability of the critical processing parameters and establish tested upper and lower limits of those parameters to demonstrate proper operation in achieving Tc99m. [page 1178].

The subject testing is completed using three (3) productions equivalent RGX systems and the final RGX software. The Sponsor states one(1) system is run 30 times with "specifically developed software protocols that isolate specific reagent delivery metrics that are identical to final elution protocol." In addition, two systems will be run a minimum of ten times per reagent line [page 1182].

Flow rate verification

The Sponsor states "Flow rate repeatability (or speed of the syringe controller) is considered a function of the [redacted] (b) (4) syringe and is not deemed to be a factor for repeatability analysis. It will however be tested as a factor for robustness in the following section; and as such, it will be tested beyond its limits/specifications. The following information describes the syringe controller specifications and resulting accuracy to determine the assignable flow rate repeatability. The speed is set [redacted] (b) (4)

Volume Repeatability

"Volume repeatability will test the three main reagent delivery paths. This encompasses all tubing lines which carry the reagents through the chromatography column (the PSC) to a respective final point of delivery. The saline path is not considered to be a critical volumetric path in determining the elution chromatography process."

Specifications Limits Testing for Volume and Flow
In addition to the volume testing desrcibed above the all three systems are run 32 while applying flow rate and volume limitation boundaries. The run parameter were established using a Taguchi stastical analysis method (page 1190). The following table listed the reagent flow and volume specifications:

Kinked line verification
The Sponsor states "The intent of this testing is to demonstrate that if a normal kink occurred due to handling, that the system would fail in a safe mode. Since this is due to system interface and handling, the majority of the testing will occur on those lines which the user has access to during normal operations. Lines which are enclosed by a special key, primarily for entrée by NMR service only, will not be tested. All lines that are "exposed" to the customer shall be tested for simulated kinks. Perform the following kinks one at a time, and record observed operation during a COLD Elution using sterile water as the media for all reagents."

In summary, the Sponsor states the system can function as intended if an accessible line is kinked. One test demonstrated that tube kinking between a Source vessel and the Rotating valve would prevent proper flow of the "cold source material" and cause the system to generate an error and prevent further use without service from the Sponsor.

7. DISCIPLINE SPECIFIC SUB-CONSULTED REVIEW

The information below is from consult memos. In summary, the device is considered acceptable for dispensing the radioactive technetium (TC-99m) solution as intended, however mechanical engineering and consults recommend post market commitments.

7.1. Discipline 1 (Mechanical Engineering)

The following is extracted from the consult Prasanna Hariharan's memo:

> Northstar LLC submitted the New Drug Application (NDA) for the TechneGen generator system to produce short-lived radioactive technetium (TC-99m) from longer lived radioactive Molybdenum (Mo-99) solution. The final TC-99m product will be used as a radiopharmaceutical agent for diagnostic imaging procedures. The system uses a resin filter to separate TC-99m from the parent Mo-99 (which has traces of TC-99m). Subsequently, the retained technetium gets washed from the filter using saline solution. The equipment is a "flow-based system" with a micro-processor controlled flow-loop to transport the parent and daughter fluids, and the cleaning agents. I reviewed the fluid flow aspects of the TechneGen system and identified deficiencies that can potentially affect the safety and effectiveness of the device. CDRH's concerns were communicated with the applicant during the teleconference held on May 22nd, 2013. The sponsors responded to FDA's deficiency early this year (2017). Two additional rounds of interactive review were performed to address the flow-based issues in their system.

The two main issues with their system was the i) possibility of the occlusion/clog in the system which could reduce the effectiveness of the separation process. The occlusion could also lead to leakage of radioactive substance from the system due to high pressure in the fluid lines ii) possibility of leaks in the system due to improper connection between fluid lines or between fluid line and the valve network. After raising these issues, the sponsors added a pressure sensor to the system that can detect and warn the user if the pressure exceeds (b) (4) psi in the fluid lines. The pressure sensor can directly or indirectly detect clogs or occlusion in majority of the fluid pathways inside the system. They also have introduced multiple mitigation measures to minimize the risks for leaks inside the system. These measures include line-integrity testing during installation and FIT testing (for leaks) during the device operation before supplying the radioactive substance through the pathways. Consequently, the sponsors responded to the occlusion and leak related deficiencies in a satisfactory manner.

As a part of the review, we also requested the sponsor to evaluate how the flow rate of various solutions and the elution process is affected by the aging of the device. They had mentioned that majority of the flow components will be replaced every year. For components that are replaced every year, the functional testing needs to be done to only demonstrate reliability and functionality throughout this duration (i.e 1 year). The sponsor proposed (b) (4) The lead reviewer is recommended to consult with the other shelf-life experts to make this decision.

In addition, taking it to consideration the complexity of their system**, I recommend that the sponsor do the following post market study during the annual maintenance check of each one of their systems**

1. Identify and detail all locations of occlusion, clog or deposit buildup in the fluid lines including the valves

2. Identify and detail all locations of leak noticed in the system

This information is required to ensure that the long-term durability of the system is acceptable and the performance of the system does not degrade with time.

7.2. Discipline 2 (Software)

The following is extracted from the consult Joseph Jorgen III memo:

1. Level Of Concern: Acceptable
In Section 4.1 entitled Level Of Concern the firm provided the correct determination of the level of concern and included their supporting rationale: MODERATE.

2. Software Description: Acceptable

In Appendix 2 entitled Software/Firmware Design Specifications the firm provided an acceptable comprehensive overview of the device features that are controlled by software, and a description of the intended operational environment, which includes information on the programming language, the hardware platform, the operating system and the use of Off-The-Shelf software.

3. Device (including software) Hazard Analysis: Acceptable
In Appendix 8 entitled Validation in Sections entitled Risk Mitigation Effectiveness Test and Risk Estimation and Risk Control the firm provided an acceptable description of the hazards presented by this device, the causes and severity of the hazards, the method of control of the hazards and the testing done to verify the correct implementation of that method of control, and any residual hazards.

4.Software Requirements Specifications (SRS): Acceptable
In Appendix 8 entitled Validation in Sections entitled Specification Traceability Matrix and in Appendix 3 entitled Functional Customer Requirements the firm provided acceptable Software Requirements Specifications which clearly documented the functional, performance, interface, design and development requirements.

5. Architecture Design Chart: Acceptable
In Appendix 2 entitled Software/Firmware Design Specifications in Section 7.0 the firm provided an acceptable detailed depiction of functional units and software modules, which included state diagrams as well as flow charts.

6. Software Design Specification (SDS): Acceptable
In Appendix 2 entitled Software/Firmware Design Specifications the firm provided acceptable Software Design Specifications which describes how the requirements in the Software Requirements Specifications (SRS) are implemented.

7. Traceability: Acceptable
In Appendix 8 entitled Validation in the Section entitled Specification Traceability Matrix the firm provided acceptable traceability among identified hazards and mitigations, requirements, specifications, and verification and validation testing.

8. Software Development Environment Description: Acceptable
In Appendix 2 entitled Software/Firmware Design Specifications in Sections 8 and 9 the firm provided an acceptable description of the software development environment, which included a summary of the software life cycle development plan, and a summary of the configuration management and maintenance activities.

9. Verification and Validation Documentation: Acceptable

In the original submission and in Appendix 8 entitled Validation the firm provided an acceptable description of the validation and verification activities at the unit, integration and system level, which included system level test protocols, including the pass/fail criteria, and the results of these activities.

10. Revision Level History: Acceptable
In Appendix 9 entitled Software and Firmware Revision History the firm provided an acceptable revision history log, which provides the history of software revisions generated during the course of product development.

11. Unresolved Anomalies (Bugs or Defects): Acceptable
In Appendix 8 entitled Validation in the Section entitled Residual Software Anomalies the firm provided an acceptable list of the remaining software anomalies, annotated with an explanation of the impact of the anomaly on safety or effectiveness, including operator usage and human factors.

12. Cyber and Information Security: N/A

13. Run-Time Error Detection: Acceptable
The firm stated that they do not use any static analysis tool to detect software run-time errors. Because this section is intended to inform the firm that we are now interested in the use of static analysis tools and to collect data on their current use, this response is Acceptable.

RECOMMENDATION: APPROVAL

The firm has provided acceptable documentation demonstrating that they have developed the software for this device under appropriate software development program; that they have performed a hazard analysis from both the patient's and user's standpoint, and addressed those hazards; and carried out an appropriate validation process. These procedures provide the foundation for assuring, to the extent possible, that the software will operate in a manner described in the specifications, and in no other way. It is recommended that from a software standpoint this submission be approved.

7.3. Discipline 3 (EMC)

The following is extracted from the consult Donald Witter's memo:

Summary:
The EMC and wireless information in this response submission provides generally reasonable information to earlier deficiencies concerning EMC testing and the wireless technology

incorporated into the Tc99m device system. The sponsor has [redacted] (b) (4) I noted a minor point in the recommended separation distance values that should be rounded to the nearest centimeter from the several significant digits in the proposed operator manual information. Not clear if this was mentioned in previous reviews but it should be addressed by the sponsor: because the Tc99 device that was tested by ICL required modifications to pass the EMC immunity testing the sponsor should provide a clear statement all the modifications will be included in the production units.

After Sponsor's response with labeling updates:
I believe the EMC and wireless portion have been resolved.

7.4. Discipline 4 (Electrical Safety)

Electrical Engineer Michael Long completed review of DMF 026592 and in summary considers **the documentation sufficient for demonstrating the electrical safety of the device**.

On 01/08/18 the electrical safety consultant confirmed that there were no outstanding review issues concerning the electrical safety of the system:

Deficiency1: The problem was that the sponsor has submitted two different Test Reports:

1. IEC 61010-1 Edition 3.0 2010-06, IEC 61010-1 Edition 3.0 2010-06, safety requirements for electrical equipment for measurement, control, and laboratory use - part 1: general requirement.

2. IEC 60601-1: 2005 + CORR. 1 (2006) + CORR. 2 (2007) Test Report (Reference: Master File 26592, CSA Group test report IEC 60601-1 Medical electrical equipment Part 1: General requirements for basic safety and essential performance.)

The problem was that those two standards are mutually exclusive. As stated in IEC 61010-1: In Section 1.1.2, "Equipment excluded from scope"

"This standard does not apply to equipment within the scope of:
a) IEC 60065 (Audio, video and similar electronic apparatus);
b) IEC 60204 (Safety of machinery – Electrical equipment of machines);
c) IEC 60335 (Household and similar electrical appliances);
d) IEC 60364 (Electrical installations of buildings);
e) IEC 60439 (Low-voltage switchgear and controller assemblies);
f) IEC 60601 (Medical electrical equipment)"

Therefore: The sponsor can only claim that their device is either a medical device or laboratory equipment.

Deficiency 2: This is more of a documentation problem. In the IEC 60601-1: 2005 + CORR. 1 (2006) + CORR. 2 (2007) standard, the manufacturer is allowed to determine whether the medical device has any "essential performance." Clinicians are not always in agreement with that change in the recent version of the standard. I usually have the clinicians make the final decision.

Therefore: The IEC 60601-1: 2005 + CORR. 1 (2006) + CORR. 2 (2007) Test Report is what we needed. The IEC 61010-1 Edition 3.0 2010-06, IEC 61010-1 Edition 3.0 2010-06 is not applicable to this medical device.

Based on what I stated above, the medical device is electrically safe.

7.5. Discipline 5 (Human Factors)

Human Factors is reviewed by DMEPA, and was also reviewed by consult Dr. Shannon Hoste. The paragraph below summarizes Dr. Hoste's review. After review and discussion during a face-to-face demonstration of the device, the **Lead Reviewer considers the human factor concerns mentioned below successfully addressed by the Sponsor through labeling warnings. CDER/OSE/DMEPA also provided comments to the Sponsor regarding recommended labeling updates.**

You have provided your Human Factors Validation report. While your Human Factors validation study method is sound; it is not clear that the analysis is complete. Your study identified several use errors and difficulties with following the safety protocols. You identified issues with the use of survey meters, inappropriate radioactive waste disposal, TPC and shielding insertion, system leakage, inappropriate response to system leakage of radioactive materials, inappropriate assembly of reagent kits, failure to wipe the loaders before installing a new PSC, errors on several sterilization steps, difficulties with the screen selections and confusion over the red Stop Button and the Stop Protocol button. Each of these has been evaluated and considered from your overall product risk assessment; however, given the prevalence of these use errors and difficulties in your simulated use study, it is not clear that modifications to the user interface (including training and labeling) would not further reduce risk or are not possible or practicable.

After subsequent discussion with the Sponsor the above concerns were resolved according to the Lead Reviewer and labeling warnings adequately mitigated the concerns of the human factors study failures.

8. RISK ANALYSIS

8.1. Risk Analysis Attributes

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	X		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	X		
Mitigations are adequate to reduce risk to health	X		
Version history demonstrates risk management throughout design / development activities	X		

8.2. Summary of Risk Analysis

The Sponsor provides a risk analysis for the subject system beginning on PDF page 1310 of document "a1-facilities-and-equipment" with GSR 026592/ m3. The analyses include a list of hazards, associated likely causes, control methods, and associated verification references. The hazards identified are listed in the following categories: Energy Hazards, Biological Hazards, Environmental Hazards, and Functional Failures/ Maintenance/ Aging (page 1371).

The Functional Failure, Maintenance, Aging Failure, hazards are subject of this review. The list identifies hazards associated with the system user and the patient. Note, no failure of the system is a direct risk to the patient as the final solution is only available for use after verification from a certified radioactivity lab. Risks of exposure to the user are considered by the Sponsor, and the mitigation methods appear acceptable. The Sponsor has verified exposure due to normal use is prevented through the system components. The verification to demonstrate the system will not leak, and controls function to prevent leak is adequately verifies unexpected exposures are controlled.

9. LABELING

The subject label is an extensive document located in GSR sequence 0033 section 1.14., and is reviewed by CDER and DMEPA.

(b) (4)

Reviewer note:
A review of the labeling to understand the product, and ensure the instructions align with functions identified is completed. No labeling changes are recommended.

10. DESIGN TRANSFER ACTIVITIES – RELEASE SPECIFICATION

The subject device is shipped and installed at its final destination by the Sponsor's qualified personnel. The device is set up and evaluated by the setup personnel to verify all features and functions operate as intended. The final setup samples are verified by third party facilities to ensure the finished solution is within established software specifications.

11. OUTSTANDING DEFICIENCIES

N/A

12. RECOMMENDATION

The Sponsor adequately demonstrates the device constituents can reliably extract Sodium pertechnetate Tc99m from a Mo99/Tc99m generator system, thus CDRH recommends approval with post market commitments.

12.1. Recommended Post-market commitments/post-market requirements

Taking it to consideration the complexity of your flow path, we recommend that you do the following post market study during the annual maintenance check of each one of your systems:

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 by the software.
4. Report any elution volumes which are out of tolerance.

This information is required to ensure that the long-term durability of the system is acceptable and the performance of the system does not degrade with time.

13. APPENDIX

The Following is a compilation of all consult review memos:

13.1. Electrical Safety (Michael Long)

13.2. EMC/Wireless (Donald Witters)

Summary: The EMC and wireless information in this response submission provides generally reasonable information to earlier deficiencies concerning EMC testing and the wireless technology incorporated into the Tc99m device system. The sponsor has (b) (4) I noted a minor point in the recommended separation distance values that should be rounded to the nearest centimeter from the several significant digits in the proposed operator manual information. Not clear if this was mentioned in previous reviews but it should be addressed by the sponsor: because the Tc99 device that was tested by ICL required modifications to pass the EMC immunity testing the sponsor should provide a clear statement all the modifications will be included in the production units.

Update on 01/08/18 with Sponsor's Response to above concern:

NorthStar's Response: The EMC modifications are currently included in the existing product and current submission as evidenced by the associated engineering assembly drawing revisions and BOM.

The following EMC information shall be truncated and included/updated in the User's Manual as shown in the following table:

Max Output Power (Watts)	Separation (m) 150kHz to 80 MHz D=(3.5/V1)(Sqrt P)	Separation (m) 80MHz to 800MHz D=(3.5/E1)(Sqrt P)	Separation (m) 800MHz to 2.5GHz D=(37/E1)(Sqrt P)
0.01	0.12	0.12	0.23
0.1	0.37	0.37	0.74
1	1.17	1.17	2.33
10	3.69	3.69	7.38
100	11.67	11.67	23.33

NorthStar acknowledges that wireless coexistence, and appropriate testing are important and will be assessed and included in future submissions.

Device Description and intended use: The NorthStar RadioGenix System is a compact, automated radionuclide system that separates High Specific Activity (HSA) technetium-99m (Tc-99m) from Low Specific Activity (LSA) molybdenum-99 (Mo-99). The RadioGenix System efficiently and reproducibly prepares sterile Sodium Pertechnetate, Tc-99m Injection, USP for patient use from its longer-lived parent, molybdenum-99. The RadioGenix System has five subsystems: workstation, instrument, cabinet, ozone generator, and uninterruptible power supply (UPS). The RadioGenix workstation consists of a computer and touchscreen. The workstation includes an application workstation and a software application. The application runs on the application workstation and provides the user interface to communicate with the instrument. The RadioGenix instrument houses pumps, valves, fluid lines, shields, and control electronics. The nuclear pharmacy replaces the reagent, sterilization, and product collection kits. NorthStar services the instrument. The cabinet contains the molybdenum Mo-99 (source) vessels and the discarded materials containers. The nuclear pharmacy replaces these items on a routine basis. The cabinet also houses the transfer vessel and it is serviced by NorthStar. The ozone generator produces ozone in water for weekly sterilization of the instrument. The uninterruptible power supply (UPS)/battery backup for the instrument provides power in the case of facility power loss. The UPS only supplies 115 VAC.

Scope of Review: The information in the September 2017 responses, DMF (b) (4) DMF Information Request, 1.11.1 Quality Information Amendment, pages 1 through 10, specifically points 2 and 3 focuses on EMC and wireless technology information was reviewed. These responses are in reference to deficiencies sent to the sponsor on July 12, 2017 and appear to be based on my July 6, 2017 review memo. .

Response Reviews:

1. Response to deficiency point 3. Original deficiency: In summary, on about July 12, 2017, the Agency previously asked "Please explain and justify the EMC testing on only a portion of the Tc99m system". Your response claims the system "was tested to meet CISPR 11 which includes emissions and immunity". The

CISPR 11 Ed 5.1, 2010 standard "Industrial, scientific and medical equipment – Radiofrequency disturbance characteristics - Limits and methods of measurement" specifically addresses electromagnetic disturbances emitted by the equipment being measured; it does not address immunity. As stated in the previous deficiency the computer equipment should be assessed for electromagnetic compatibility (EMC) that covers both emissions and immunity. The FCC part 47 requirements, and the CISPR 22 (essentially equal to EN55022), EN 55011 (essentially equal to CISPR 11) standards all address emissions only, and have generally the same emissions limits though the CISPR 11 is specific for medical equipment and can be more stringent in certain areas. The response is therefore only partially adequate. You should amend claims that CISPR 11 covers immunity and justify that the computer equipment meets the appropriate EMC standards. Alternatively, if all computer equipment, including accessories, was included in the device that was tested, or you are able to show that the computers meet emissions and immunity appropriate to their device then please provide adequate information and justification to resolve this point.

Review: The response states that the sponsor recognizes their error in claiming the CISPR 11 standard includes immunity and point back to the ICL report on the Tc99 EMC testing, which included a PC. The response is adequate.

2. Response to deficiency point 4. Original deficiency: Your response to the previous deficiency, reiterated below in italicized text, indicates that you believe testing and compliance with the CISPR 11 standard adequately covers EMC for the computer equipment used in or with the RadioGenix Tc99 device system. This is incorrect because the CISPR 11 standard is applicable to emissions from the equipment and does not address immunity. Therefore, please provide clear evidence that the computer equipment integrated into or used with your device adequately meets all appropriate EMC standards for emissions and immunity to interference. Reference to the CISPR 22 and 24 standards that were mentioned in the deficiency or equivalent is recommended. If the testing purported in the ICL EMC report done in reference to IEC 61326-1 included all of the computer equipment specified to be used with the Tc99 device you should be able to leverage this information to support your claims. You should also note that in many computer manufacturers perform the CISPR 24 standard immunity testing or equivalent. Previous Deficiency: "The information in your response includes EMC related emissions testing for the computer component of the TC99m device system referenced to FCC and CE requirements. However, this does not fully address qualifications for the component or the EMC immunity for safety and effectiveness. Please provide complete information about the description and qualifications for the computer component required in the TC99m device system. This should include adequate EMC qualification information and testing for the computer components to demonstrate that both emissions and immunity are fully addressed via appropriate standards such as CISPR 22 and 24."

Review: The information in the ICL test report indicates that a PC and computer periphery components were used during the EMC tests. Additional information indicates the PC components meet the CISPR 22 and 24 standards. Thus, the computer equipment seems to have been adequately tested. The response is adequate for this portion. However, if not already address the sponsor should provide a clear statement that the modifications needed to pass the EMC testing will be included in all the production units.

3. Response to deficiency point 5. Original deficiency: The proposed additional warning information regarding EMC generally seems helpful. However, the recommendation to (b) (4) is inadequate because the user will not generally have access to this document or be able to find and use it when needed. In addition, the statement recommending that the Tc99 device system be (b) (4) from disturbance sources is inadequate. Therefore, please add summary information about specific electromagnetic environment and recommended separation distances from electromagnetic emitters based on the EMC test results where you intend your device to be used. A good reference for guidance for this information is the IEC 60601-1-2 standard, which contains guidance about specific environments and separation distances based on the EMC testing that you should be able to leverage for the TC99 device system labeling.

Review: The response admits the error in citing the EN 61000-2-3 standard for the user to help reduce the chances for EMI and proposes adding information to the manual that summarizes the EMC testing and includes information in the Operator guide, 94S05058 Rev 03-A, page v. This information includes the values for the recommended separation distances based on the frequency and output power of the external emitter. The new information seems reasonable. However, the values in the separation distance table should be truncated/rounded to the nearest centimeter.

4. Response to deficiency point 6. Original deficiency: "The response information generally seems reasonable about the proposed information to be added to the device labeling. However, your statement about the CISPR 11 covering EMC immunity is incorrect and should be changed because this standard is applicable to emissions only. In addition, please make the following changes to your proposed labeling additions.

a. Change the information for Wi-Fi to have the security recommendations on a separate line. Add a statement about the Bluetooth Discovery mode and how this is secured to prevent unauthorized access. In addition, you should be aware of a recent potential threat to Bluetooth enabled equipment called Blueborne with can be attacked via Bluetooth Classic implementations.

b. Please address how you intend to assess and if needed mitigate the Tc99 device system against Blueborne.

c. Change to the information about the integrated RFID components to add a separate line for security information.

d. Please provide a final version of the labeling that highlights the changes."

Review: The response information and labeling is adequate to address the wireless technology deficiency points.

5. Response to deficiency 7. Original deficiency: "Previously the Agency requested you "perform adequate wireless coexistence testing to assure safety and performance of the Tc99m device system and submit the results. For your reference, you might consider consulting the recently published AAMI Technical Information

Report TIR69:2017 Risk management of radio-frequency wireless coexistence for medical devices and systems." The response provided needs additional clarifications, because, the EMC test standards such as IEC 61326 do not adequately address risks associated with wireless issues such as coexistence. Please change any labeling or other statements that claim standards other than the C63.27 standard address wireless coexistence.

Review: The response states the sponsor declares the RadioGenix Tc99 as not a medical device and thus the TIR69 and C63.27 do not relate. While the TIR69 is aimed at medical devices the principles can be applied to the Tc99 type of device, and indeed, the sponsor did this by performing a risk analysis for the wireless technology and functions. While the sponsor has some reason to deal with the TIR in this manner they are incorrect about the C63.27 standard as no applicable because this standard is applicable to most wirelessly enabled products. Nevertheless, the response and previous information are acceptable at this point. However, the sponsor should be informed that the issue of wireless coexistence is important and the TIR69 and C63.27 are available tools to address this issue.

13.3. Software (Joseph Jorgens)

Succinct Conclusion: APPROVE

The information contained within this submission is sufficient to meet the software concerns as described in the Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices, and it is recommended that, from a software standpoint, this submission be approved.

SUMMARY:

Northstar LLC submitted the New Drug Application (NDA) for the TechneGen generator system to produce short-lived radioactive technetium (TC-99m) from longer lived radioactive Molybdenum (Mo-99) solution. The final TC-99m product is used as a radiopharmaceutical agent for diagnostic imaging procedures. The system uses a resin filter to separate TC-99m from the parent Mo-99 (which has traces of TC-99m). Subsequently, the retained technetium gets washed from the filter using saline solution. The equipment is a "flow-based system" with a micro-processor controlled flow-loop to transport the parent and daughter fluids, and the cleaning agents.

The TechneGen is the equipment part of the TechneGen Generator System (TGS) instrument used to produce Tc99m for use as a sodium pertechnetate, Tc99m imaging agent and for preparation of a number of Tc99m labeled radiopharmaceutical agents used in diagnostic imaging procedures. The TGS receives Mo99 that is produced by a nuclear reactor or linear accelerator and converts it into concentrated sodium pertechnetate, Tc99m injection, suitable for preparing Tc99m labeled diagnostic imaging agents for a variety of diagnostic imaging procedures.

The TechneGen Generator System is a microprocessor-controlled instrument for use by a radioactive material (RAM) authorized practitioner and/or trained nuclear pharmacist, This chemical separation system may be used to quickly and efficiently prepare a high purity daughter radioisotope of suitable chemical and pharmaceutical quality for use in diagnostic imaging procedures or to prepare radiotherapy agents. The TechneGen Generator System has been specifically designed to process sodium pertechnetate Tc99m and facilitates the purification and handling of the parent-daughter radioisotope pair Mo99 /Tc99m to produce a high purity solution of sodium pertechnetate Tc99m Injection USP. The TechneGen Generator System has been uniquely developed to efficiently, routinely, and reproducibly separate high purity short-lived Tc99m from its longer lived parent, Mo99.

The TechneGen Generator System consists of three major physical components.

The first component is the host computer running the custom application software using the Microsoft .NET architecture.

The second is the instrument itself which houses an assortment of pumps, valves, fluid lines, radiation shielding, sensors, indicators and control electronics.

The third component is the chemistry reagents and separation cartridges that are designed specifically to coordinate the required sequences and methods for isotopic separation.

Software Controlled Aspects of the Device

All components of the device are controlled/monitored by software, which is responsible for the functionality, user interface, safety checks and performance accuracy.

SOFTWARE REVIEW

1. **Level Of Concern: Acceptable**
   In Section 4.1 entitled Level Of Concern the firm provided the correct determination of the level of concern and included their supporting rationale: MODERATE.

2. **Software Description: Acceptable**
   In Appendix 2 entitled Software/Firmware Design Specifications the firm provided an acceptable comprehensive overview of the device features that are controlled by software, and a description of the intended operational environment, which includes information on the programming language, the hardware platform, the operating system and the use of Off-The-Shelf software.

3. **Device (including software) Hazard Analysis: Acceptable**
   In Appendix 8 entitled Validation in Sections entitled Risk Mitigation Effectiveness Test and Risk Estimation and Risk

Control the firm provided an acceptable description of the hazards presented by this device, the causes and severity of the hazards, the method of control of the hazards and the testing done to verify the correct implementation of that method of control, and any residual hazards.

4. **Software Requirements Specifications (SRS): Acceptable**
In Appendix 8 entitled Validation in Sections entitled Specification Traceability Matrix and in Appendix 3 entitled Functional Customer Requirements the firm provided acceptable Software Requirements Specifications which clearly documented the functional, performance, interface, design and development requirements.

5. **Architecture Design Chart: Acceptable**
In Appendix 2 entitled Software/Firmware Design Specifications in Section 7.0 the firm provided an acceptable detailed depiction of functional units and software modules, which included state diagrams as well as flow charts.

6. **Software Design Specification (SDS)**: **Acceptable**
In Appendix 2 entitled Software/Firmware Design Specifications the firm provided acceptable Software Design Specifications which describes how the requirements in the Software Requirements Specifications (SRS) are implemented.

7. **Traceability: Acceptable**
In Appendix 8 entitled Validation in the Section entitled Specification Traceability Matrix the firm provided acceptable traceability among identified hazards and mitigations, requirements, specifications, and verification and validation testing.

8. **Software Development Environment Description: Acceptable**
In Appendix 2 entitled Software/Firmware Design Specifications in Sections 8 and 9 the firm provided an acceptable description of the software development environment, which included a summary of the software life cycle development plan, and a summary of the configuration management and maintenance activities.

9. **Verification and Validation Documentation: Acceptable**
In the original submission and in Appendix 8 entitled Validation the firm provided an acceptable description of the validation and verification activities at the unit, integration and system level, which included system level test protocols, including the pass/fail criteria, and the results of these activities.

10. **Revision Level History: Acceptable**
In Appendix 9 entitled Software and Firmware Revision History the firm provided an acceptable revision history log, which provides the history of software revisions generated during the course of product development.

11. **Unresolved Anomalies (Bugs or Defects): Acceptable**
In Appendix 8 entitled Validation in the Section entitled Residual Software Anomalies the firm provided an acceptable list of the remaining software anomalies, annotated with an explanation of the impact of the anomaly on safety or effectiveness, including operator usage and human factors.

12. **Cyber and Information Security: N/A**

13. **Run-Time Error Detection: Acceptable**
The firm stated that they do not use any static analysis tool to detect software run-time errors. Because this section is intended to inform the firm that we are now interested in the use of static analysis tools and to collect data on their current use, this response is Acceptable.

RECOMMENDATION: APPROVAL

The firm has provided acceptable documentation demonstrating that they have developed the software for this device under appropriate software development program; that they have performed a hazard analysis from both the patient's and user's standpoint, and addressed those hazards; and carried out an appropriate validation process. These procedures provide the foundation for assuring, to the extent possible, that the software will operate in a manner described in the specifications, and in no other way. It is recommended that from a software standpoint this submission be approved.

13.4. Mechanical Engineering (Prasanna Hariharan)

Review Summary **There are no deficiencies related to this submission**.

Scope

This review covers the fluid flow aspects of the TechneGen generator system

Review Summary

Northstar LLC submitted the New Drug Application (NDA) for the TechneGen generator system to produce short-lived radioactive technetium (TC-99m) from longer lived radioactive Molybdenum (Mo-99) solution. The final TC-99m product will be used as a radiopharmaceutical agent for diagnostic imaging procedures. The system uses a resin filter to separate TC-99m from the parent Mo-99 (which has traces of TC-99m). Subsequently, the retained technetium gets washed from the filter using saline solution. The equipment is a "flow-based system" with a micro-processor controlled flow-loop to transport the parent and daughter fluids, and the cleaning agents. I reviewed the fluid flow aspects of the TechneGen system and identified deficiencies that can potentially affect the safety and effectiveness of the device. CDRH's concerns were communicated with the applicant during the teleconference held on May 22nd, 2013. The sponsors responded to FDA's deficiency early this year (2017). Two additional rounds of interactive review were performed to address the flow-based issues in their system.

The two main issues with their system was the i) possibility of the occlusion/clog in the system which could reduce the effectiveness of the separation process. The occlusion could also lead to leakage of radioactive substance from the system due to high pressure in the fluid lines ii) possibility of leaks in the system due to improper connection between fluid lines or between fluid line and the valve network. After raising these issues, the sponsors added a pressure sensor to the system that can detect and warn the user if the pressure exceeds (b) (4) psi in the fluid lines. The pressure sensor can directly or indirectly detect clogs or occlusion in majority of the fluid pathways inside the system. They also have introduced multiple mitigation measures to minimize the risks for leaks inside the system. These measures include line-integrity testing during installation and FIT testing (for leaks) during the device operation before supplying the radioactive substance through the pathways. Consequently, the sponsors responded to the occlusion and leak related deficiencies in a satisfactory manner.

As a part of the review, we also requested the sponsor to evaluate how the flow rate of various solutions and the elution process is affected by the aging of the device. They had mentioned that majority of the flow components will be replaced every year. For components that are replaced every year, the functional testing needs to be done to only demonstrate reliability and functionality throughout this duration (i.e 1 year). The sponsor proposed (b) (4) The lead reviewer is recommended to consult with the other shelf-life experts to make this decision.

In addition, taking it to consideration the complexity of their system, I recommend that the sponsor do the following post market study during the annual maintenance check of each one of their systems

1. Identify and detail all locations of occlusion, clog or deposit buildup in the fluid lines including the valves

2. Identify and detail all locations of leak noticed in the system

This information is required to ensure that the long-term durability of the system is acceptable and the performance of the system does not degrade with time.

Review of sponsor's response to FDA's deficiencies

Round 1 (deficiencies sent on May 2013)

1. Original deficiency:

Please install pressure sensors within the flow loop, or justify why such sensors are not necessary. Include in your justification scenarios where a valve may close shut or a tube may kink, causing pressure to rise.

Sponsor's response:

In response to this deficiency, the sponsors have installed a pressure sensor inside the flow circuit. The exact location of the pressure sensor is shown in Figure below

Figure 2: Schematic of the RGX instrument with the pressure sensor located in (b) (4)

Figure 3 below shows that the pressure sensor located (b) (4)

Figure 3: Flow circuit showing the location of the pressure sensor

In addition, the sponsors have stated that the RGX system will issue an advisory message when the pressure is greater than (b) (4) psi and will interlock the system (which will require service intervention) if the pressure is (b) (4) psi or greater.

Review of sponsor's response:

The sponsor's response to the deficiency is not acceptable. The following additional details need to be provided by the sponsor to ensure that the pressure sensor is located in the appropriate location New Deficiency#1

1. Please justify how a single pressure sensor is enough to measure the pressure and evaluate the

performance of the entire flow network. If the circuit is not completely serial, the pressure sensor may not detect the presence of leaks, clogs, and kinks in regions that are cut-off from the sensor. In page 791 of the submission, you identified the location of the pressure sensor in the flow circuit of the device. It looks like the pressure sensor is (b) (4). If this part of the line is shut-off from the rest of the flow circuit, the pressure sensor cannot detect the line pressure for the rest of the system. Please clarify how you intend to monitor the system pressure when the pressure sensor is cut-off from the rest of the circuit during certain duration of the device operation.

2. Please clarify how the pressure threshold of (b) (4) psi was obtained. In page 795 of the DMF#26592, you have stated that for the PSC filter to work efficiently, the line pressure should not exceed (b) (4) psi. If the flow loop is clogged or leaking at various locations, please clarify if the pressure threshold of (b) (4) psi will be able to capture the malfunction, stop the elution/cleaning and warn the user in an appropriate and timely manner

3. In page 2424 of your submission, you mentioned a test protocol for detecting the fluid pathway leaks in the system when the RGX system is newly installed. This test used a pressure kit test which was connected to different parts of the loop to detect for leak. Please clarify if similar testing will be performed periodically during the lifetime of the device to ensure the integrity of the flow pathways.

2. Original deficiency

Please describe measures taken to reduce the likelihood of kinks, both external and internal to the instrument.

Sponsor's response

In order to address this deficiency, the sponsors have included the following mitigation measures

a. They enlarged the size of the whole system to allow for larger bend radii and additional tubing length to further reduce strain on the tubing connections when they are installed or replaced.

b. The installation procedure now prompts field installation personnel to visually inspect factory installed lines for kinks as well as to inspect the field installed lines before and after installation.

c. The customer access to these tubing lines is completely eliminated. The Service Door and Transfer

Door have a uniquely keyed lock that is different than the user accessible Source & Discarded Material Doors. Only service personnel are intended to access these two bays that contain the valves and majority of tubing connections.

Review of sponsor's response

The sponsor's response to this deficiency is not acceptable. The sponsors have identified mitigation measures to avoid kinking during the installation of the device. They should also discuss the possibility of the kinks occurring during the use of the device and identify appropriate mitigation measures. If the sponsor thinks that the probability of kinking is very low during the device operation, they should state that explicitly in the submission (New Deficiency#2).

3. Original Deficiency

Please perform experiments where you occlude the tubing to simulate a kinked tube or valve failed close. Please provide pressure measurements and observations of system response. The duration of observation should be long enough that the steady-state response of the system occurs, e.g. that which would occur if no one was available to immediately intervene.

Sponsor's response:

In response to this deficiency, the sponsors performed testing to show that if a normal kink occurred due to handling, the system would fail in a safe mode. Six different sections of tubing, that are more susceptible to user kinks due to accessibility, were kinked one at a time, and then an elution executed. During testing of Five (5) of the kinked lines, the elution process was observed to execute properly and no pressure errors were detected indicating that pressure remained below (b)(4) psi. During the final kinked line test, a filter integrity failure was logged by the instrument. The kinked line for this test was between Source Vessel 2 (SV2) and Rotating Valve 3 (RV2). Kinking this line prevented the proper amount of cold Mo source material to be drawn from the source vessel. This testing shows that if this line were to become kinked in actual use, the system software will interlock the instrument due to failure of the filter integrity test and indicate that the instrument is not available for use.

Review of the sponsor's response:

The sponsor's response to this deficiency is inadequate. The new deficiency is enclosed below

In response to deficiency#3 you performed the occlusion testing on flow-lines that are only exposed to the user. Consequently, only six small sections of the flow-circuit were chosen for the occlusion testing. Our intention was to evaluate how the system will respond to occlusion (due to clogging, and kinking etc) in any part of the flow network. The occlusion due to clogging can occur on lines that are internal and not exposed to the user. So, please test if the device will

fail in a safe mode due to occlusion in key parts of the flow circuit (New Deficiency#3).

4. Original deficiency

Please provide measures of product quality over a wider range of flow rates than the factor of two already investigated. Provide the range of flow for which product quality is acceptable.

Sponsor's response

In response to this deficiency, the sponsors performed repeatability study to estimate the Upper and Lower Specification Limits (USL and LSL) for each of the Elution variability factors such as the flow rate and volume of KOH, NaAc , and H2O2 solutions. Based on the analysis, the sponsors have listed the following upper and lower specification limits for the flow rate as (Table 1)

Variability	(b) (4)
Volume LSL - USL	
Flow LSL - USL	

Table 1: Specification limits for flow rate and volume

Review of the sponsor's response

The sponsor's response to this deficiency is inadequate. They have looked in to the effect of flow rate in terms of the repeatability of the elution process. Their results showed that the flow rates of various reagents are fairly repeatable and the elution process was successful when the flow rates are within USL and LSL. In addition, we also need the following information to ensure that the elution process is safe and effective over the entire lifetime of the device (New Deficiency#4)

- Please evaluate how the flow rate of various solutions and the elution process is affected by the aging of the device. You had mentioned that majority of the flow components will be replaced every year. For components that are replaced every year, the functional testing needs to be done only during that duration (i.e 1 year). The testing could be done in accelerated manner as long as all the elution and cleaning steps are properly followed. In addition, this test can be done for the entire device instead of

doing the testing for each individual component.

5. Original deficiency

Please provide the minimum, maximum, and average flow rate likely to occur through all valves and membranes. Please also provide engineering drawings for each type of valve.

Review of sponsor's response:

The sponsors have responded to this deficiency in an acceptable manner. They have provided the upper and lower specifications limits for flow rates. In addition , they have provided the engineering drawings of all the valves

New Deficiencies:

1. In response to Deficiency#5, you have attached a pressure sensor inside the device. However, the following additional details need to be provided to ensure that the pressure sensor is located in the appropriate location

   - Please justify how a single pressure sensor is enough to measure the pressure and evaluate the performance of the entire flow network. If the circuit is not completely serial, the pressure sensor may not detect the presence of leaks, clogs, and kinks in regions that are cut-off from the sensor. In page 791 of the submission, you identified the location of the pressure sensor in the flow circuit of the device. It looks like the pressure sensor is (b) (4) If this part of the line is shut-off from the rest of the flow circuit, the pressure sensor cannot detect the line pressure for the rest of the system. Please clarify how you intend to monitor the system pressure when the pressure sensor is cut-off from the rest of the circuit during certain duration of the device operation.

   - Please clarify how the pressure threshold of (b) (4) psi was obtained. In page 795 of the DMF#26592, you have stated that for the PSC filter to work efficiently, the line pressure should not exceed (b) (4) psi. If the flow loop is clogged or leaking at various locations, please clarify if the pressure threshold of (b) (4) psi will be able to capture the malfunction, stop the elution/cleaning and warn the user in an appropriate and timely manner

- In page 2424 of your submission, you mentioned a test protocol for detecting the fluid pathway leaks in the system when the RGX system is newly installed. This test used a pressure kit test which was connected to different parts of the loop to detect for leak. Please clarify if similar testing will be performed periodically during the lifetime of the device to ensure the integrity of the flow pathways.

2. In response to deficiency#6, you have listed several mitigation measures to avoid kinking during the installation of the device. In addition, please discuss the possibility of the kinks occurring during the use of the device and identify appropriate mitigation measures. If you think that the probability of kinking is very low during the device operation, please state that explicitly in the submission. Please clarify if you performed usability study with potential users to understand and obtain feedback related to the risk for kinking inside the device.

3. In response to deficiency#7 you performed the occlusion testing on flow-lines that are only exposed to the user. Consequently, only six small sections of the flow-circuit were chosen for the occlusion testing. Our intention was to evaluate how the system will respond to occlusion (due to clogging, and kinking etc) in any part of the flow network. The occlusion due to clogging can occur on lines that are internal and not exposed to the user. So, please test if the device will fail in a safe mode due to occlusion in key parts of the flow circuit.

4. In response to deficiency#8, you looked in to the effect of flow rate on the repeatability of the elution process. Your results showed that the flow rates of various reagents are fairly repeatable and the elution process was successful when the flow rates are within USL and LSL. However, In addition to this data, we also need the following information to ensure that the elution process is safe and effective over the entire lifetime of the device

    - Please evaluate how the flow rate of various solutions and the elution process is affected by the aging of the device. You had mentioned that majority of the flow components will be replaced every year. For components that are replaced every year, the functional testing needs to be done only during that duration (i.e 1 year). The testing could be done in accelerated manner as long as all the elution and cleaning steps are properly followed. In addition, this test can be done for the entire device instead of doing the testing for each individual component.

Round 2 (deficiencies sent on Aug 2017)

Deficiency#1:

Please justify how a single pressure sensor is enough to measure the pressure and evaluate the performance of the entire flow network. If the circuit is not completely serial, the pressure sensor may not detect the presence of leaks, clogs, and kinks in regions that are cut-off from the sensor. In page 791 of the submission, you identified the location of the pressure sensor in the flow circuit of the device. It looks like the pressure sensor is connected (b) (4) . If this part of the line is shut-off from the rest of the flow circuit, the pressure sensor cannot detect the line pressure for the rest of the system. Please clarify how you intend to monitor the system pressure when the pressure sensor is cut-off from the rest of the circuit during certain duration of the device operation.

NorthStar Response:

Although the pressure sensor appears to be isolated in a single tubing segment, it is systemically exposed to the active fluid path lines during operation. Due to the dynamic nature of the fluid system, line failures during one portion of an elution not directly in contact with a sensor, may be detected at a later step in the elution process. The attached Tubing DFMEA analysis and report identifies the breadth of mitigations in place to address tube occlusions, kinks, and leaks. In addition to the pressure sensor, the line radiation sensor is used to directly measure radioactive fluid flow. Beyond this, there are multiple other mitigations employed to ensure performance of the fluid network.

Review of the response

In response to FDA's deficiency, the sponsors stated that failures in fluid lines that are not in direct contact with the sensor may be detected in the later step of the elution process. To demonstrate this, the sponsors provided an example scenario where the occlusion in the saline line (not directly in contact with the pressure sensor) was detected by the pressure sensor later in the protocol as a FIT test failure. In addition, the sponsors also include the DFMEA analysis that lists the breadth of mitigation measures put in place to address tube occlusions, kinks, and leaks.

The sponsor's response to this deficiency is **not acceptable**. The new deficiencies after reviewing the sponsor's response is provided below

New Deficiency#1: In response to deficiency#4a, you stated that failures in fluid lines that are not in direct contact with the sensor may be detected in the later step of the elution process. To demonstrate this, you provided an example scenario (Figure#2 and 3 in Report#90RPT09482) where the occlusion in the saline line (not directly in contact with the pressure sensor) was detected by the pressure sensor later in the protocol as a FIT test failure. You also provided other scenarios where the pressure sensor directly contacts the fluid line (Figure#4-7). However, your response does not clearly say if the pressure sensor can directly or indirectly predict occlusion/clogging in **all** the fluid lines. If you claim that the pressure sensor can detect the occlusion/clogs in all fluid lines, even if not in direct contact with the line, please

demonstrate that using multiple examples. In your response, you demonstrated this capability using only one example.

New Deficiency#2: Please discuss why the pressure sensor could not be used for detecting the leaks. As of now, the pressure sensor is only used to check if the line pressures exceed an upper limit of (b) (4) psi. In theory, the same sensor could be used to check if the line pressures fall below a lower limit indicative of leakage. The FDA believes that there are no active mitigation measures currently in place to detect/address leaks in your system. The current mitigation measure for leaks, as listed in your DFMEA analysis, include one or all of the following i) meeting tube material specification to avoid leaks ii) limiting access to the interior tubes and iii) annual service maintenance. These mitigation measures are passive in nature i.e. meant to prevent the leak either during installation or during annual maintenance. None of these mitigation measures can detect and address leaks during the device operation. In order to ensure the safety and effectiveness of the equipment, the device should be equipped to detect leaks in **all** the fluid lines during the operation and should dynamically shutdown or modify the elution process and avoid any potential harm to the operator. Please discuss how your system can detect and handle leaks in all the fluid lines during the elution and cleaning processes.

Deficiency#2:

Please clarify how the pressure threshold of (b) (4) psi was obtained. In page 795 of the DMF#26592, you have stated that for the PSC filter to work efficiently, the line pressure should not exceed (b) (4) psi. If the flow loop is clogged or leaking at various locations, please clarify if the pressure threshold of (b) (4) psi will be able to capture the malfunction, stop the elution/cleaning and warn the user in an appropriate and timely manner

NorthStar Response:

Please allow us to clarify page 795: The four bullet points document the four separate and distinct uses of the pressure sensor during protocols.

The first bullet documents the (b) (4) and tests the integrity of the flow path between (b) (4) .

The second bullet documents the Filter Integrity Test (FIT) used during elution. The product (b) (4) pressure, which is the maximum pressure the system can experience without warning, and below the (b) (4) This ensures the filter has not been compromised after usage. (b) (4)

The third bullet documents the continuous monitoring use of the pressure sensor during protocols, whereby any pressure level sensed greater than (b) (4) psi and less than (b) (4) psi results in a user advisory.

The fourth bullet documents the continually monitored use of the pressure sensor during protocols, whereby any pressure level sensed greater than (b)(4) psi results in a system fault (protocol aborted or system interlock with service call required, see DMF page 16).

The (b)(4) psi threshold mentioned in the 4th bullet was chosen because it is above the peak pressure of (b)(4) psi used during normal operation (reference DMF page 16), but dramatically lower than the pressure generated due to syringe push against an occlusion (syringe fault occurs at (b)(4) psi, while tubing/connections are rated in the thousands of psi). The (b)(4) psi threshold is applicable to a clogged condition, however, is not applicable to a leaking condition, as a leak to ambient would tend to lower pressure. Leakage failure modes are considered and addressed as noted in the attached DFMEA.

Review of the response: The new deficiencies listed for deficiency#4a is applicable to this deficiency

Deficiency#3

In page 2424 of your submission, you mentioned a test protocol for detecting the fluid pathway leaks in the system when the RGX system is newly installed. This test used a pressure kit test which was connected to different parts of the loop to detect for leak. Please clarify if similar testing will be performed periodically during the lifetime of the device to ensure the integrity of the flow pathways.

NorthStar Response:

A validated full system pressure test of all the lines is done every year during annual planned maintenance. This service test more extensively tests pressure than the test on page 2424 of the DMF. The test on page 2424 of the DMF is a manufacturing subsystem test and only applies to the upper portion of the RGX (the portion of the system shown on page 14 of the DMF). “RGX W-TEST” refers specifically to that upper subassembly. Full testing of all lines within the RGX system to the validated service pressure test procedure occurs at the user site, at installation where the RGX W-TEST is assembled into the RGX system with all tubes connected, and annually during planned maintenance and when any service operation is performed.

Review of the response:

The sponsor’s response is acceptable. They have clarified that the pressure tests will be done annually for all the lines

Deficiency#4

In response to deficiency#6 (Discussed during a teleconference held on May 22nd, 2013), you listed several mitigation measures to avoid kinking during the installation of the device. In addition, please discuss the possibility of the kinks occurring during the use of the device and identify appropriate mitigation measures. If you think that the probability

of kinking is very low during the device operation, please state that explicitly in the submission. Please clarify if you performed usability study with potential users to understand and obtain feedback related to the risk for kinking inside the device.

NorthStar Response:

Since the May 22nd 2013 teleconference we have designed out access to the majority of previously accessible lines. These lines are now locked behind service doors. The remaining accessible lines were tested with kinks in the robustness test and shown safe as the fluid was able to push kinks open. In addition, reference the Tubing DFMEA to show safe failure in every kinked line condition in the event of a full kink. Since there are no moving parts and user access to the vast majority of lines is blocked, the likelihood of the user kinking lines is dramatically lower than the risk of kinking during manufacture or installation. Which is why we (b) (4) during production and at installation. HFE (Appendix M) testing with multiple users in actual use conditions found no observed kinking of the remaining accessible tubes.

Review of the response:

The sponsor's response is acceptable. The sponsors performed usability study and found no observed kinking of the accessible tubes.

Round 3 (deficiencies sent on Oct 2017)

1. In response to deficiency#4a, you stated that failures in fluid lines that are not in direct contact with the sensor may be detected in the later step of the elution process. To demonstrate this, you provided an example scenario (Figure#2 and 3 in Report#90RPT09482) where the occlusion in the saline line (not directly in contact with the pressure sensor) was detected by the pressure sensor later in the protocol as a FIT test failure. You also provided other scenarios where the pressure sensor directly contacts the fluid line (Figure#4-7). However, your response does not clearly say if the pressure sensor can directly or indirectly predict occlusion/clogging in all the fluid lines. If you claim that the pressure sensor can detect the occlusion/clogs in all fluid lines, even if not in direct contact with the line, please demonstrate that using multiple examples. In your response, you demonstrated this capability using only one example.

NorthStars Response: The pressure sensor by itself does not detect occlusions/clogs in all fluid lines. The combination of the radiation sensor and the pressure sensor does provide the capability to detect occlusions/clogs in the radioactive fluid lines (discussed in more detail below). In the case, of non-radioactive lines (saline, reagent, and air inputs), the occlusion or clogging is detected indirectly by a later step in the process (as defined in the DFMEA). Two examples are noted below.

For question 1 to the most recent NDA Information Request dated October 26, 2017 NorthStar included a series of flow path diagrams present during elution (and in addition to figures 4-7 of the report# 90RPT09482) which indicates the various flow paths where the pressure sensor is in the active fluid path. During all steps the pressure sensor is monitoring for pressures > (b) (4) psi which may indicate occlusion of the fluid path, excluding the (b) (4) step and (b) (4) step where the system is (b) (4)

(b) (4).

The pressure sensor can directly or indirectly sense an occlusion/clogging in the radioactive fluid lines within the system via the over-pressure protections – with the exception of the line to the source vessels. However in this case, the radiation sensor predicts the presence of an occlusion, as the system checks to ensure it sees radiation from fluid movement during this (b) (4) step. Non-radioactive fluid lines consist of the lines from the reagents assembly (peroxide, acetate, and hydroxide), saline, and the air lines. In each of these cases the pressure is balanced with the ambient environment (via reagent bags, saline syringe, and air filter), and the use of the pressure sensor to detect occlusion is impractical, and therefore we don't claim the pressure sensor is able to detect occlusion / clogs in all fluid lines.

In our DFMEA report, we provided one example where an occlusion in the saline line is detected indirectly by a later step, (b) (4). An additional example of this indirect detection would be during the (b) (4) test, (b) (4) An occlusion between the (b) (4) and the (b) (4) would not be detected immediately when a (b) (4). These cases are exceptions that indicate additional capability not explicitly stated in the NDA.

(b) (4)

Figure #1 – (b) (4)

Review of the response

The sponsors response is acceptable. They have provided enough information to show that the pressure sensor can be used to directly or indirectly detect occlusion or clog in majority of the fluid lines. However, taking it to consideration the complexity of their system, we recommend that the sponsor do the following analysis as a post market study during the annual maintenance check

1. Identify and detail all locations of occlusion, clog or deposit buildup in the fluid lines including the

valves

2. Identify and detail all locations of leak noticed in the system

This information is required to ensure that the long-term durability of the system is acceptable and the performance of the system does not degrade with time.

2. Please discuss why the pressure sensor could not be used for detecting the leaks. As of now, the pressure sensor is only used to check if the line pressures exceed an upper limit of (b) (4) *psi. In theory, the same sensor could be used to check if the line pressures fall below a lower limit indicative of leakage. The FDA believes that there are no active mitigation measures currently in place to detect/address leaks in your system. The current mitigation measure for leaks, as listed in your DFMEA analysis, include one or all of the following i) meeting tube material specification to avoid leaks ii) limiting access to the interior tubes and iii) annual service maintenance. These mitigation measures are passive in nature i.e. meant to prevent the leak either during installation or during annual maintenance. None of these mitigation measures can detect and address leaks during the device operation. In order to ensure the safety and effectiveness of the equipment, the device should be equipped to detect leaks in all the fluid lines during the operation and should dynamically shutdown or modify the elution process and avoid any potential harm to the operator. Please discuss how your system can detect and handle leaks in all the fluid lines during the elution and cleaning processes.*

NorthStars Response: There are several key flow paths where the pressure sensor can and is used to detect leaks (Discussed below). This is detected in cases where the pressure fails to achieve the expected value during specific tests. However there are multiple lines in the RadioGenix System that are vented (for example: lines to the Source Vessels and Waste Container). Since they are vented, they cannot be expected to maintain pressure and the sensor cannot see the difference between a leak and normal venting. Because of this, the RadioGenix System has been designed so that leak detection is not required to prevent harm to the operator.

To avoid potential harm to the operator from leaks, NorthStar has designed the device using risk management principles and redundancy in design to provide layers of protection against harm to the operator from leaks.

- The first layer of protection against harm to the operator from leaks is by the use of proven fluid transfer components at pressures well below their rated capability, using proven materials, limiting access to connections, employing a maintenance procedure which replaces components yearly, and employing service/installation pressure tests to ensure the integrity of the fluid path. This first layer of protection ensures that if a leak occurs, it would be rare.
- The second layer of protection against harm to the operator from leaks is through the use of a shielded enclosure. This enclosure ensures that if leaks occur that their severity will be significantly limited, and the likelihood of this layer failing is extremely low (shielding is inherent to the system design).
- The third layer of protection against harm to the operator from leaks is by radiation measurement prescribed in our training, operator's guide, and quick guides, as well as pharmacy practice. The use of radiation detectors to regularly survey the device when using the RadioGenix to perform an elution is included in the operator's guide, quick guide videos, and training. Pharmacy practice includes general radiation awareness, badging, as well as area monitoring of radiation levels.

These protections form the passive layers used by the RadioGenix to protect the operator from harm caused by leaks. NorthStar believes their inherent redundancy is an effective means of protecting the operator from harm of leaks, because

a failure of this system of protection against leaks would require triple fault failure.

Further, the RadioGenix system does employ the pressure sensor using two active methods to protect against leaks.

- The first active method is the (b) (4) test. This occurs during step (b) (4), whereby (b) (4) Leaks in this flow path will be directly detected.
- The second active method is the FIT test. This occurs during step (b) (4), and (b) (4) (see *figure 2* below). Leaks in this flow path will be directly detected.

Figure 2 – Fluid path for FIT test step during elution protocol

Where the pressure sensor is not used to actively detect leaks is in the fluid lines connecting to the source vessel, transfer vessel, discarded material, air lines, and reagent lines. In all of these cases, the pressure is balanced with ambient conditions, making use of the pressure sensor to detect leaks impractical or unreliable. However, this also means those lines are not under pressure beyond the minimal pressure required to move the fluids. This lowered pressure also reduces the risk of leaks in those lines, as there is significantly less pressure to push fluid out any leakage pathway.

Review of the response

The sponsors response is acceptable. They have provided enough mitigation measure to ensure safety of the user if there is a leak in the system. However, takin it to consideration the complexity of their system, we recommend that the sponsor do the following analysis as a post market study during the annual maintenance

check

1. Identify and detail all locations of occlusion, clog or deposit buildup in the fluid lines including the valves
2. Identify and detail all locations of leaks in the system

This information is required to ensure that the long-term durability of the system is acceptable and the performance of the system does not degrade with time

Final recommendation to the sponsor

Taking it to consideration the complexity of your flow path, we recommend that you do the following post market study during the annual maintenance check of each one of your systems

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

This information is required to ensure that the long-term durability of the system is acceptable and the performance of the system does not degrade with time

13.5. Human Factors (Shannon Hoste)

HF Recommendation: THIS IS FEEDBACK FOR THE LEAD REVIEWER, to communicate if there is a concern over exposure/safety protocols:

You have provided your Human Factors Validation report. While your Human Factors validation study method is sound; it is not clear that the analysis is complete. Your study identified several use errors and difficulties with following the safety protocols. You identified issues with the use of survey meters, inappropriate radioactive waste disposal, TPC and shielding insertion, system leakage, inappropriate response to system leakage of radioactive materials, inappropriate assembly of reagent kits, failure to wipe the loaders before installing a new PSC, errors on several sterilization steps, difficulties with the screen selections and confusion over the red Stop Button and the Stop Protocol button. Each of these has been evaluated and considered from your overall product risk assessment; however, given the prevalence of these use errors and difficulties in your simulated use study, it is not clear that modifications to the user interface (including training and labeling) would not further reduce risk or are not possible or practicable.

Reviewers Notes

Regulatory/Interaction History
Related ICC: ICC1700052

From NDA 202158 TechneGen Generator System Complete Response.pdf issued 11/04/2013:

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

Device Description
Because of the unique ability to extract and concentrate Tc-99m from dilute solutions of Mo-99 in potassium molybdate, the RGX has the potential to obviate requirement of production of high concentration Mo-99 manufactured by fission of U235. NorthStar seeks approval from the Food and Drug Administration (FDA) of this instrument/process. A New Drug Application (NDA) was submitted (NDA 202158) to the FDA on January 4, 2013 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TechneGen Generator System (TGS) the precursor for the RGX, for Preparation of Sodium Pertechnetate Tc-99m Injection. As a result of the comments obtained from the FDA's Complete Response Letter (ID 3401347) to the submission, NorthStar undertook a project to significantly redesign the TGS (Figure 1) to address the issues raised. The new instrument was re-launched as the RGX (Figure 2) with the expectation that the changes made and resulting confirmation testing will address the agency's concerns prior to providing the Final Amendment to the NDA Submission.

HF Activities

From a1-facilities-and-equipment.pdf page 49/2485:

A two-phase approach to the human factors evaluation of the Mo-99/Tc-99m instrument and associated training program (Phase I - Formative Evaluation; Phase II – Summative). An independent organization (b) (4)) facilitated the Human Factors Evaluation (HFE) for NorthStar. This included all activities as described in the scope and approach section below. NorthStar provided the sites, participants, training materials, operation guides and the RadioGenix Systems for inclusion in this study. Additionally NorthStar performed the training as defined by NorthStar's training program, RadioGenix User Training, pn 94S05898. Other than providing all materials needed for the evaluation, including training, NorthStar did not participate in any way during the final Summative HFE testing.

A formative evaluation was implemented to improve the usability of the RadioGenix System, operational guide and training program. A formative evaluation period was conducted where experts and potential users provided human factors feedback on the RGX to improve its design prior to a summative study (validation testing). Summative usability evaluation was the final validation intended to demonstrate that all risks have been identified and adequately addressed and that the impact of residual risks were minimized and acceptable. Summative evaluation maintained a focus on the RGX in its intended environment while attended by its

intended user groups. This evaluation followed the FDA draft guidance (Applying human factors and usability engineering to optimize medical device design).

The heuristic evaluation, use-related risk analysis, and findings from the formative and summative usability evaluations have been consolidated into a final report, located in Appendix 8.

Human Factors Evaluation Conclusion: Through human factors methods including heuristic evaluation, risk analysis, labeling comprehension, and both formative and summative testing, (b) (4) found the RGX to be safe and effective for the intended users, uses, and use environments.

From a1-facilities-and-equipment.pdf appendix 8, starting on page 1275/2485:

The Human Factors Evaluation starts on page 1594/2485.

INTENDED USERS, USES, USE ENVIRONMENTS & TRAINING

All nuclear pharmacists and nuclear pharmacy technicians using the RGX must receive instructions and training prior to using the system with radioactive materials. The basis for successful use is safely and correctly performing all seven system protocols in accordance with the training and instructions. The purpose of the effort described in this document is a human factors evaluation of the training program and instructional material that prepares an individual to safely and effectively perform the protocols. Therefore, this section will briefly describe the training program and the procedures prior to presenting information related to the human factors evaluation approach in subsequent sections. The training program and all associated materials (i.e. Operator's Manual, instructional videos, labeling) utilized during the human factors evaluation will represent the final versions that will be marketing for commercial use. It is important to note that post-elution quality assessments will also be performed; however, these user tasks will not be evaluated as part of the human factors evaluation as they are related to the end-product quality and are not covered in training.

The training program is to be conducted over a four to six-hour period. Each training session will have two trainers from NorthStar instructing no more than eight trainees at one time in order to facilitate appropriate training. There are three primary training components designed for this program: 1) lecture/presentation on system operation, 2) hands-on training with a simulated RGX to be incorporated with the lecture, 3) a trial run of a radioactive separation and simulated trial runs of the six other protocols run on the system. The program alternates between these elements in order to assure maximum retention of training. For instance,

if trainees are being instructed on how to install a reagent kit, they are first given information on the procedure by the trainers through a PowerPoint presentation and video, and then given the opportunity to practice the procedure on a simulated RGX. Training on other tasks follows the same format…

After completion of the lecture and hands-on practice portions, a complete run-through of the seven protocols that can be run on the system will be performed by the subjects. The procedure will begin with the system in a newly-installed state and end after all protocols have been completed. Since the order of execution of the protocols will not be consistent in the field, the order of performance of the protocols will be determined by logistics rather than any concern for order effects…

This training program will be conducted by NorthStar during initial installation of the RGX. Any subsequent new users of the RGX who did not participate in the initial training will receive the same onsite training by NorthStar as described above.

Reviewer Analysis/Comments: Further information on users and use environment is provided in the sponsor document. This information is aligned with what is requested in the Agency guidance on applying human factors for medical devices.

DEVICE USER INTERFACE

Reviewer Analysis/Comments: Further information on the user interface is presented starting on page 1745 of 2485. This information is aligned with what is requested in the Agency guidance on applying human factors for medical devices.

KNOWN USE PROBLEMS, FORMATIVE, IDENTIFICATION OF CRITICAL TASKS

(b) (4)

Prior to developing the summative usability testing protocol, two use-related risk analyses were performed: 1) for the TGS, and 2) for the RGX. These risk analyses were performed by personnel from (b) (4) with assistance from subject-matter experts in the nuclear pharmacy field. The purpose of this effort was to identify potential hazards associated with use of the instruments. A Failure Mode and Effects Analysis of usage (Use FMEA) was applied to identify potential hazards.

User tasks with high RPNs are considered more risky and therefore more critical for evaluation during the summative usability evaluation. Because it is often not possible to accurately predict the probability of occurrence and detection, it is relevant to focus the identification of critical tasks on the severity of potential harm. Findings from the Use FMEA performed for the RGX indicate critical tasks that will be of primary focus (highest 20 percent of severity ratings) for the summative study.

- Produce Tc-99m Protocol

o Remove scrub cap from saline port or spent saline syringe

o Clean saline port with scrub cap

o Remove new saline syringe from package
o Install saline syringe to saline port by twisting
o Unthread bottom of vial shield
o Remove product vial from packaging o Wipe septum of vial with alcohol wipe o Insert product vial into vial shield
o Install bottom of vial shield
o Remove Tc-99m product cartridge from package
o Remove spike cover from Tc-99m product cartridge
o Insert Tc-99m product cartridge into shield by pressing down to puncture septum
o Dispose of scrub cap as radioactive waste
o Wipe product port with alcohol wipe
o Dispose of alcohol wipe as radioactive waste
o Remove plug from top of Tc-99m product cartridge
o Insert shield assembly into product loader
o Select "Continue" on software interface to proceed with protocol
o Allow RGX system to run separation protocol
o Remove shield assembly from RGX
o Dispose of Tc-99m product cartridge as radioactive waste
o Cap vial shield with tungsten cap
o Cap product port
o Allow RGX system to complete protocol
o Take vial shield to kitting area

- Exchange Discarded Material Container Protocol

o Remove the container from the system by disconnecting container from bulkhead
o Install the tethered luer cap on the container
o Remove the tethered luer cap from the container
o Remove the cap from the bulkhead
o Clean bulkhead connection with wipe
o Connect the Discarded Material container to the system

- Change Reagent Kit Protocol

o Ensure user is wearing all appropriate personal protective equipment
o Remove reagent assembly from packaging
o Remove scrub caps from reagent port or spent reagent module
o Remove plugs from tubing connectors
o Dispose of primary separation cartridge as radioactive waste
o Clean primary separation cartridge loaders with alcohol wipes
o Dispose of alcohol wipes as radioactive waste
o Disengage PSC loaders by moving levers left or right o Remove primary separation cartridge from packaging
o Remove plugs from primary separation cartridge

- Sterilization Protocol

o Wipe air filter port with alcohol wipe
o Remove air filter from packaging
o Install air filter by twisting onto port
o Unthread bottom of vial shield
o Install bottom of vial shield
o Remove spike cover from blank Techetium Product Column (TPC)
o Insert blank TPC cartridge into shield, pressing down to puncture septum
o Insert shield assembly into RGX
o Select "Continue" on software interface to proceed with protocol (occurs 3 times during protocol)
o Remove scrub caps or reagent connections from reagent port
o Connect saline ozone tube to saline port

o Clean ozone tubing holders with scrub caps
o Connect ozone tubes to holders
o Place scrub caps on reagent ports
o Remove shielded assembly from product port
o Dispose of blank Tc-99m product cartridge as radioactive waste
o Unthread bottom of vial shield
o Reinstall threaded vial shield bottom
• Remove Source Protocol
o Select ""Continue" on software interface to proceed with protocol
o Disconnect catheter from bulkhead
o Cap catheter with luer cap o Cap bulkhead with luer cap o Pull out source tray
o Unlock manifold and pull catheter slightly away from source vessel
o Remove Mo-99 source vessel from tray
• Add Source Protocol
o Pull out source tray
o Place Mo-99 source vessel on tray o Remove manifold from packaging o Install manifold on source vessel o Remove air filter from packaging o Remove catheter from packaging o Remove blue cap from bulkhead o Remove cap from catheter
Reviewer Analysis/Comments: Further information on the heuristic analysis, formative studies and FMEA is provided in the sponsor document. Note further discussion of critical tasks can be found starting on page 1770/2485. This information is aligned with what is requested in the Agency guidance on applying human factors for medical
devices.

HF VALIDATION STUDY PROTOCOL & METHOD

Summative usability evaluation is the final validation method intended to demonstrate that all risks have been identified, adequately addressed and that the impacts of residual risks are minimized. Summative evaluation

conducted by (b) (4) will focus on evaluating the training program in its intended environment while the intended user groups attend. The summative study protocol was refined to take into account results of the formative work. All previous tests and evaluations helped to refine the training program design. Therefore, the training program shall be in its final form and ready for validation in a real-world environment…
Before each participant's validation testing, an RGX will be prepared to mimic how a system would appear after initial install by NorthStar. Participants will perform all activities that would routinely be conducted as part of performing Mo-Tc separations, including installing all necessary kits and running all necessary software protocols.

Multiple usability sessions will be run depending on the size of each testing facility and the availability of equipment. If multiple RGX systems are onsite, and multiple participants can be tested simultaneously without influencing the performance of neighboring participants, then testing of multiple participants will be performed concurrently.

Each summative usability evaluation will occur over the course of two days per participant, and will consist of 1) signing of necessary documents by participants; 2) participating in the training program in groups of no more than 8 participants per training session; 3) a decay period of a minimum of 12 hours; 4)

participants returning after the decay period for validation of user performance, 5) semi-structured interviews to evaluate training modules, materials, and lab procedures; and 6) debriefing and compensation arrangement. Each summative session will last approximately 9 hours in total, with the four to six-hour training session taking place on the first day and the three-hour validation testing occurring within the next several days…

Through direct observation, as well as video/audio data reduction and analysis, usability test measures will be taken to evaluate that the procedures are being performed safely and as intended. Both performance data and participant feedback will be collected. Independent variables (IVs) and dependent variables (DVs) of interest and the different levels of each are presented below (the level of acceptability and correctness with regards to these measures will be determined based on feedback from nuclear pharmacy subject- matter experts in collaboration with usability experts)…

For data regarding errors, the focus will be on critical task errors. These are errors that occur during any task identified as critical through the Use FMEA (the top 20 percent of severity ratings). Additionally, errors that are committed during performance of any non-critical task that could result in a serious safety risk will also be considered critical errors. Errors will be analyzed to determine the potential consequences of the error and whether or not the error would present a safety risk in a real-world situation. Participants who complete a protocol without committing any critical, irrecoverable errors with be given a "pass" rating for that protocol. If an error is determined to be irrecoverable (it was not recognized and resolved by the participant and the effects of the error could not be mitigated), then the participant will be given a "fail" rating for that protocol…

Reviewer Analysis/Comments: Further information on the HF validation method is provided in the sponsor document. This information is aligned with what is requested in the Agency guidance on applying human factors for medical devices.

HF VALIDATION STUDY RESULTS
The study consistent of 15 nuclear pharmacists and 15 nuclear pharmacy technicians. The technicians were current PharmD students who, as part of their university requirements, are qualified technicians in a licensed facility. The technicians' years of study in the nuclear pharmacy field ranged from 1 to 3.5 years (mean of 2.0 years), and technician age ranged from 21 to 39 years, with a mean age of 24.7. Many technicians had experience working in nuclear pharmacies for internships or conducting research as part of their education, and some others only had experience through classroom learning. The range of nuclear pharmacy experience for the pharmacists ranged from 4 months to 32 years (mean of 15.2 years), with ages ranging from 24 to 66 years, with a mean age of 44.2. The majority of pharmacists were currently practicing, while others had transitioned to managerial or corporate positions.

- Scenario #1: Initialization had no critical tasks

- Scenario #2: Add Source Vessel

o Two technicians experienced minor struggles with the install of the manifold and had to remove and reattach it multiple times before attaching correctly. Neither error resulted in the identified critical failure mode of damaging the manifold, which could compromise the material quality if installed on the source vessel while damaged.

o Two pharmacists omitted the task of surveying the door for radiation before opening it. Although these omissions would not have resulted in the critical consequence of radiation exposure during the

testing, it is possible that this could be the case in real life even if the probability of occurrence is very low. When debriefed about these errors, both participants stated that using the survey meter is a normal part of their everyday practice and that the training and instructional materials were clear on when the meter needed to be used… Due to the artificial constraints of the study contributing to this omission and the use of the survey meter as a standard procedure in nuclear pharmacies, this error was not considered to be a critical, irrecoverable error that would constitute a scenario failure.

- Scenario #3: Remove Source Vessel

o As with Scenario #2, several pharmacists omitted the task of surveying the source door. Two of them were the same participants who committed the error during Scenario #2, and the third gave similar statements as the others in the debrief.

o for the task of unlocking the manifold and pulling it away from the vessel…these were minor errors of commission and not considered critical failure modes. Two of the 3 participants recognized their error in the debrief without prompting from the moderator on the specific failure mode.

o The additional critical task errors recorded during this scenario were also minor in consequence. One participant committed an aseptic error by dropping the luer cap before capping the bulkhead, which would only result in minor, inconsequential contamination if any. The additional errors occurring during steps 3.8 and 3.9 were corrected and recovered from.

o Because no critical, irrecoverable errors were committed that could lead to harmful consequences, all participants received a pass rating for Scenario #3.

• Scenario #4: Produce Tc-99m Protocol (Perform Elution)

o Of the 26 critical tasks, 17 were performed without error by any of the participants. Again, failing to utilize the survey meter before opening a system door was associated with several errors, but they were committed by the same participants who omitted the task during Scenarios #1 and #2, with the addition of one pharmacist who recognized they forgot to perform the task and felt the training and instructional materials were clear on the when it needs to be done.

o Several participants also disposed of radioactive waste as regular waste during tasks 4.28 and 4.30. Although the severity of improper disposal was rated highly in comparison to other tasks because of the potential contamination hazard, the amount of radioactivity is very low and exposure would be minimal. During follow-up, one technician described the location of the disposal bins as a possible factor in the error. The simulated nature of the study dictated that disposal bins could not be identical to what would normally be provided in a nuclear facility, which could lead to slips or unintended errors.

o Additional critical task errors occurring during elution were minor and not indicative of critical consequences. Two pharmacists initially attempted to insert the shielding backwards before selfcorrecting and inserting the shielding properly. One failed to wipe the product port with (b) (4) before inserting the shielding, but the resultant risk would be minor at worst (based on NorthStar's internal Risk Analysis, see 1.4 for a discussion of the differences between (b) (4) Risk Analysis and that performed by NorthStar) and not affect product quality.

o Another critical task error that a participant recognized before it could cause a problem occurred during the insertion of the TPC into the shielding. The participant attempted to insert the TPC into

the shielding backwards and applied enough force to result in a snapping noise. The participant then corrected the error and inserted the TPC correctly, but stated that they would not use the TPC or vial

because damage may have occurred. The participant was given new materials and completed the scenario successfully.

o The two pharmacists who committed errors during disposal of the TPC did not use the tongs for disposal, but rather popped the TPC slightly out of the shielding with their thumbs. They both recognized that they did not perform the task as instructed and indicated that this is how they would do it in practice. Although these were violations of recommended procedure, the participants were not exposing themselves to additional contamination so there were no critical consequences to the error. The final two critical task errors involved technicians failing to recognize the appropriate actions to take with the vial after the elution was complete. This is likely due to their lack of experience working in a nuclear pharmacy setting, and because critical failure modes (dropping or damaging the vial, unused or wasted product due to delay in kitting) did not occur, these errors were not considered critical, irrecoverable errors.

o One additional participant committed a critical error that did not occur during a critical task. After the elution was complete, the pharmacist surveyed the product door with the meter as expected. However, the meter detected a level of radiation that was higher than normal and the pharmacist stated that the system was "screaming hot." The pharmacist proceeded to open the product door and observed leakage within the system. They then left the product door open and indicated they needed to find something to wipe up the leakage. Because this was a potentially unsafe situation, the moderator instructed the participant to close the product door before performing any further actions. After closing the product door, the pharmacist continued to try and locate appropriate materials to clean the leakage. The moderator then requested that the session be paused and called NorthStar in to assess the safety of the situation. After the incident, the participant completed the rest of the scenario successfully using another RGX system. Although no other critical errors were committed by this pharmacist during the scenario, the participant was given a "fail" rating because their actions could have caused unnecessary radiation exposure to themselves or others in the lab. During the debriefing, the participant appeared to believe that they followed protocol correctly even though participants were not instructed to open product doors if radiation was detected. The participant's lack of experience with nuclear pharmacy practice during previous years could have contributed to the observed actions. The participant practiced as a nuclear pharmacist until 2007, but had since become a vice president in the company and had not performed an elution since then. The observed performance during this scenario constituted the only failure of the scenario, and the design of the system and training program did not contribute to the error.

o One other participant experienced a leakage issue but correctly responded to it and completed the protocol successfully.

• Scenario #5: Change Reagent Kit Protocol

o Errors were again observed with omitting the use of the survey meter for many of the same participants who omitted the task during other scenarios. The issue may have been exacerbated in the cold lab because several pharmacists did not have access to a survey meter during task performance. While conducting testing at

(b) (4), meters were in short supply and were sometimes needed by employees, so an object such as an eraser or a cup was used as a simulated survey meter.

o Additional errors were also seen with improper disposal of radioactive waste. Two errors concerned improper disposal of wipes, which as stated in the discussion of Scenario #4 would not have critical consequences and cannot be further mitigated through the design of the system, training, or instructional materials. Both participants who committed the errors also recognized the proper way to dispose of the wipes during the debrief. One participant also disposed of the PSC as chemical waste rather than radioactive waste. With mitigations, the risk of this error does not exceed the threshold for further mitigation in NorthStar's risk analysis. During the debrief, the participant recognized the proper disposal technique even though they did not realize they had disposed of the PSC improperly during the study.

o Two participants also failed to wipe the loaders before installing a new PSC. One participant immediately recognized the error and stated that they would remove the PSC, wipe the loaders, and get a new PSC. The other participant recognized the appropriate actions during the debrief and demonstrated the knowledge needed to complete the task correctly. With the mitigations implemented for this error, the risk did not exceed the threshold for further mitigation in NorthStar's risk analysis.

o The final two critical task errors occurred when participants removed the saline port scrub cap unnecessarily while removing the reagent scrub caps. This was not a critical failure mode as both participants recognized the error and requested an additional scrub cap to cover the port. Several participants experienced problems related to mismatching RFID tags and incorrectly assembled reagent kits during protocol completion, but all addressed the problems appropriately and successfully completed the protocol.

o Because no critical irrecoverable errors occurred, all participants passed Scenario #5.

• Scenario #6: Exchange Discarded Materials Container Protocol

o Few critical task errors were observed during the exchange of the discarded materials container. Four participants omitted using the survey meter on the door. One technician surveyed the wrong door, then self-corrected and surveyed the right one. For the three pharmacists that omitted the step, all had committed the error during previous scenarios as explained above.

o The other four errors were committed during the disconnection of the container from the bulkhead, and all were minor and self-corrected. One technician struggled with detaching the container and required pliers to remove it (not resulting in any damage to the container or system) and the others disconnected the tube from the bulkhead rather than from the container and corrected themselves after realizing the cap and bulkhead could not be connected. One participant recognized that they performed the task incorrectly during training and the video helped them correct the error during the evaluation.

o Other minor errors occurred during non-critical tasks, including participants opening the discarded materials container door before the protocol was ready and failing to move the selector valve to activate the new container, but these errors were recognized by the system and participants were prompted to selfcorrect.

o All users received a "pass" rating for Scenario #6.

• Scenario #7: Sterilization Protocol

o Because the sterilization process involves more task steps than any other protocol, it is not surprising that participants committed more errors during this scenario than any of the other individual scenarios. Many tasks performed during the sterilization protocol are identical to those performed during other protocols, and therefore errors such as failure to survey system doors, disposing of the TPC without using tongs, and minor self-corrected errors occurring during TPC and shield assembly insertion have been described above.

o One pharmacist failed to remove the used air filter and instead installed the new air filter on top of the old one. This was not considered critical because system operation would not be effected.

o Another pharmacist failed to place scrub caps on the reagent and saline ports after sterilization, but because any protocol following sterilization would require the participant to clean the ports again before using them, any contamination would be removed at that time. The same participant also failed to clean the ozone tubing connectors with scrub caps during the sterilization procedure. Again this wasn't considered critical because the ozone tubing was replaced on the connectors after sterilization occurred, so enough time did not pass for contamination to occur. The tubing itself also contributes to cleaning the ports after it is replaced because it has just been sterilized. This participant seemed to be struggling with computer operation during the tasks, and attributed these errors in part to unfamiliarity with how to operate the computer interface.

o Finally, three participants committed errors when they were expected to select Continue on the software screen. Two of these errors were minor and were due to tasks committed out of order. In one instance a pharmacist removed the reagent module before pressing Continue, which had no effect on the protocol. Another pharmacist selected Continue before installing the TPC and shielding. This was caught by the system and after receiving an error message the participant then performed the expected tasks correctly.

o The third participant aborted the protocol after being unable to understand why the system would not continue without inserting the TPC and shielding. Although a system control was in place that repeatedly displayed an error message informing the user that the TPC was not installed, the pharmacist kept selecting Retry and eventually aborted the protocol. After restarting the protocol the participant completed the sterilization procedure successfully, so no harmful failure effects occurred and there were no wasted materials. This was the same participant described above who struggled to operate the video appropriately, but they still

said they felt the instructional materials were clear on what to do.

o Because no errors occurring during the sterilization protocol could lead to harmful consequences, all participants passed this scenario.

• Knowledge Probes

o Some participants seemed confused about the difference between the red Stop button and the Stop Protocol button on the interface, which could indicate this is a point that should be better emphasized in training. None of the participants utilized the buttons incorrectly during the evaluations, and whenever participants needed to restart a protocol they correctly used the Stop Protocol button rather than the red Stop button which generates a system fault.

Reviewer Analysis/Comments: While the study method is sound there were several use errors and difficulties with
following the safety protocols. They identified issues with the use of survey meters, inappropriate radioactive waste disposal, TPC and shielding insertion, system leakage, inappropriate response to system leakage of radioactive
materials, inappropriate assembly of reagent kits, failure to wipe the loaders before installing a new PSC, errors on
several sterilization steps, difficulties with the screen selections and confusion over the red Stop Button and the Stop Protocol button. Many of these were also discussed in the subjective data collection.

SUBJECTIVE DATA

"There were some issues with lines being reversed and the RFID that need quality control. When I pulled off the reagents and stuff came out, it needs to be better"

POST HFE STUDY CHANGES

As discussed in the Validation Plan, HFE was a complicated process requiring the complex coordination of multiple locations and various levels of subject matter experts. (b) (4) HFE was performed at a (b) (4) with radiopharmacist personnel and at (b) (4) with Radiopharmacy students qualified as radiopharmacy technicians.

Due to the constraints of the above, HFE was completed prior to the final configuration of the RadioGenix system and user protocols. As such, reviews were held to analyze the changes that were implemented after conclusion of the HFE study for the necessity for executing further studies. There were two changes made that affect the performance of the RadioGenix protocols which directly impact the way the users operate the system and thereby potentially require additional HFE testing.

…

RGX Protocol Changes that Manifest to the User

Two updates to the RadioGenix Protocols that manifest to the user were implemented after the completion of the HFE study, neither of which were incorporated in response to safety risks discovered during HFE. Below are descriptions of those changes and justifications for their acceptance without additional HFE studies based on those changes.

1. Use of hydrogen peroxide instead of (b) (4) for wiping of reagent and sterilization ports. This change does not represent novel user behavior within the Sterilization or Remove/Install Reagents protocols, but rather the use of the proven swabbing technique for the product port (utilized in the Produce Tc-99m and Sterilization protocols) applied to the reagent and sterilization ports. This change does not represent a new behavior on the part of the user, and as such, there is not a need to re-evaluate the usability of the RadioGenix for this change.

2. During the change reagents protocol, the new reagents are installed, the system is primed, and a new PSC is installed. Prior to this change, the new PSC was installed at the time of the installation of the new reagents.

This is a minor shuffling of existing steps and does not represent a new behavior nor a novel use methodology. This change does not represent new behavior on the part of the user, and as such, there is not a need to re-evaluate the usability of the RadioGenix for this change.

RadioGenix System Application software implemented post-HFE

These changes were not motivated by the results of HFE, but rather development testing, and in most cases, either did not manifest to the user, or were corrections or clarifications to messaging or displays that correct spelling or grammar. Each of these changes was reviewed in a design review and determined not to require a re-evaluation of any portion of the HFE testing.

Reviewer Analysis/Comments: They have identified the changes implemented after testing and provided justification as to why the changes do not require further HF validation.

Materials Reviewed
- a1-facilities-and-equipment.pdf appendix 8
- NDA 202158 TechneGen Generator System Complete Response.pdf

DMIP Associate Director for Labeling Review of the Prescribing Information

Product	**RadioGenix System (technetium Tc 99m generator)**
Applicant	NorthStar
Application/Supplement Number	202158
Type of Application/Submission	**505(b)(2)** with NDA 017243 UltraTechneKow as the relied upon listed drug
Is Labeling Being Converted to PLLR?	Yes
Proposed Indication(s) (if applicable)	RadioGenix™ System is a technetium Tc 99m generator used to produce sodium pertechnetate Tc 99m injection. Sodium pertechnetate Tc 99m injection is a radioactive diagnostic agent and can be used in the preparation of FDA-approved diagnostic radiopharmaceuticals.
Approved Indication(s) (if applicable)	.RadioGenix™ System is a technetium Tc 99m generator used to produce sodium pertechnetate Tc 99m injection. Sodium pertechnetate Tc 99m injection is a radioactive diagnostic agent and can be used in the preparation of FDA-approved diagnostic radiopharmaceuticals. Sodium pertechnetate Tc 99m injection is also indicated in • Adults for: Salivary Gland Imaging and Nasolacrimal Drainage System Imaging (dacryoscintigraphy). • Adults and pediatric patients for: Thyroid Imaging and Vesicoureteral Imaging (direct isotopic cystography) for detection of vesicoureteral reflux.
Date FDA Received Application	5/7/2017
Review Classification (Priority/Standard)	Standard (resubmission)
Action Goal Date	02/08/2018 (extended due to major amendment)
Review Date	1/29/2018
Reviewer	Michele B. Fedowitz

BACKGROUND

The sponsor is submitting a 505(b)(2) application for **RadioGenix System (technetium Tc 99m generator)** to produce sodium pertechnetate Tc 99m injection. The sponsor is relying on the reference listed drug, NDA 017243 UltraTechneKow. The RLD is not in PLLR format; therefore, the sponsor is converting to PLLR.

This review includes a high-level summary of the rationale for major changes to the PI as compared to the applicant's draft PI.

Product Title
Sponsor proposed
Sodium Pertechnetate Tc-99m Injection, for intravenous and instillation use

FDA Proposed:
RADIOGENIX SYSTEM (technetium Tc 99m generator)
For the production of sodium pertechnetate Tc 99m injection, USP for intravenous, intravesicular, and ophthalmic use

Reviewer's comments: Per 21 CFR 257.57(a)(2), The Highlights limitation statement should contain the proprietary name, if available, nonproprietary name (established name of drug), dosage form, and Route of Administration (ROA).

The product title was modeled after the RLD which is similar to drugs in the class. Ultra-TechneKow™ DTE (Technetium Tc 99m Generator) For the Production of Sodium Pertechnetate Tc 99m Injection.

An additional model used was: RUBY-FILL (rubidium Rb 82 generator) To produce rubidium Rb 82 chloride injection, for intravenous use

Initial US approval
The initial approval was changed from 2018, as proposed, to 1973.
Reviewer's Comments: According to 21 CFR 201.57(a)(3). This is the four-digit year in which FDA initially approved the active moiety as a NME. 1973 is the earliest listed date of FDA approval

(2) Dosage and Administration
Much of the section was modified for clarity. Repetitive information was streamlined.

Specifically, Radiation Safety-Drug Handling, Important Administration Instructions, Quality Control, and Radiolabeling of Kits were formatted to align with similar information in other radiopharmaceutical labels.

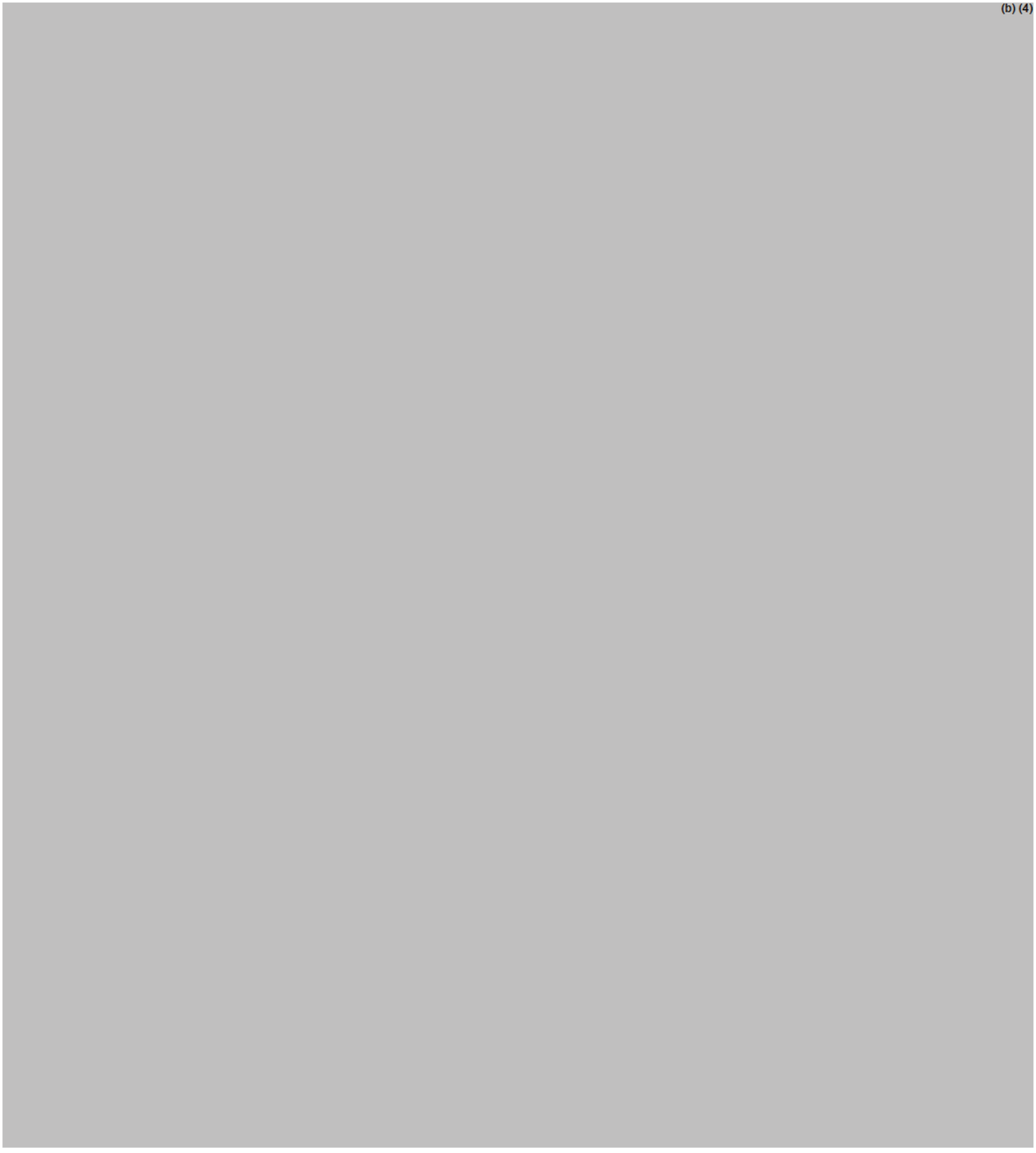
Subsections relating to the use of the system RadioGenix System Maintenance and Directions for Eluting the RadioGenix System were modified and streamlined.

Reviewer's Comments: The review team determined that there was too much information in the User Manual to adequately summarize in the Package Insert. Therefore, only pertinent use/safety information was included. The User Manual was reviewed separately and included as labeling.

2.8 Radiolabeling (Reconstitution) of Kits

Due to unique features of the system, there are volume restrictions on use for radiolabeled kits. See the Chemistry review for full details. "Use no more than 3 mL volume for radiolabeling kits with RadioGenix System-produced sodium pertechnetate Tc 99m Injection. For radiolabeling certain kits (such as Kit for the preparation of technetium Tc 99m exametazime), use no more than 1 mL volume"

2.9 Radiation Dosimetry


(b) (4)

(b) (4)

(8) Use in Specific Populations

Reviewer's Comments: The entire section was revised to comply with PLLR. Section 8.2, Lactation, was further revised with respect to the duration of interruption of breast feeding after administration based on the administered activity.

Reviewer's Comments: The duration of interruption of breastfeeding was revised based on the US Nuclear Regulatory Commission (NRC) regulation and guidance. Please refer to Dr Stanley Stern's review[9] for NDA 208870 (DRAX Exametazime) for full details. Briefly, Section 8.2, Lactation, was revised based on the NRC regulation and guidance (NUREG-1556)[10]. The regulations require medical licensees to provide instructions to nuclear-medicine patients that would limit the total effective dose equivalent (TEDE) to a nursing infant or child to not more than 1 mSv. In developing guidance for such instructions, NRC assumed that the activity released into breast milk is in the form of pertechnetate ($^{99m}TcO_4^-$), and it modeled the biodistribution of the pertechnetate as following an intravenous administration. The interruption of breastfeeding was longer than that proposed by the sponsor and represents a more conservative approach and stronger radiation-protection safeguard based on the NRC regulations.

(11) Description

11.2 Physical Characteristics
Table 2 – Principal Radiation Emission data Tc 99m: Updated[11]
11.3 External Radiation
Exposure Rate Constant and Table 3 - Radiation Attenuation by Lead Shielding: Updated[12]

(3) Dosage Forms and Strengths, (11.1) Chemical Characteristics, and (16) How Suppled Storage and Handling were reviewed by the lead Chemistry reviewer to be consistent with the RadioGenix System. The source material (non-uranium potassium molybdate Mo 99 source solution) used to produce the sodium pertechnetate Tc 99m injection, carries the NDC number. The kits for RadioGenix System are listed in the PI consistent with the user manual. The user manual was reviewed as part of labeling.

Final labeling negotiations were ongoing at the time of review. The approved label will be attached to the action letter.

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/s/

MICHELE B FEDOWITZ
01/30/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 30, 2018
Requesting Office or Division:	Division of Medical Imaging Products
Application Type and Number:	NDA 202158
Product Name and Strength:	RadioGenix System
Applicant/Sponsor Name:	NorthStar Medical Radioisotopes, LLC
FDA Received Date:	January 19, 2018
OSE RCM #:	2016-1723-1
DMEPA Safety Evaluator:	Idalia E. Rychlik, PharmD.
DMEPA Team Leader:	Hina Mehta, PharmD.

1 PURPOSE OF MEMO

Division of Medical Imaging Products requested that we review the revised Carton and Container Labels for the RadioGenix System (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised Carton and Container Labels for the RadioGenix System is acceptable from a medication error perspective. We have no further recommendations at this time.

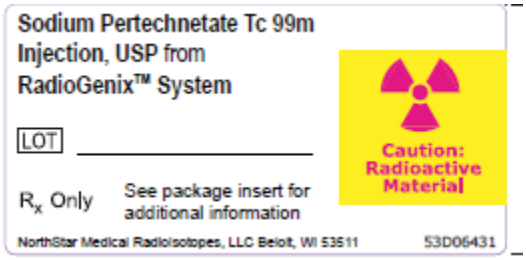
[a] Rychlik, I. Human Factors and Label and Labeling Review for RadioGenix System (NDA 202158). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JAN 12. RCM No.: 2016-1723 and 2017-1426.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JANUARY 19, 2018

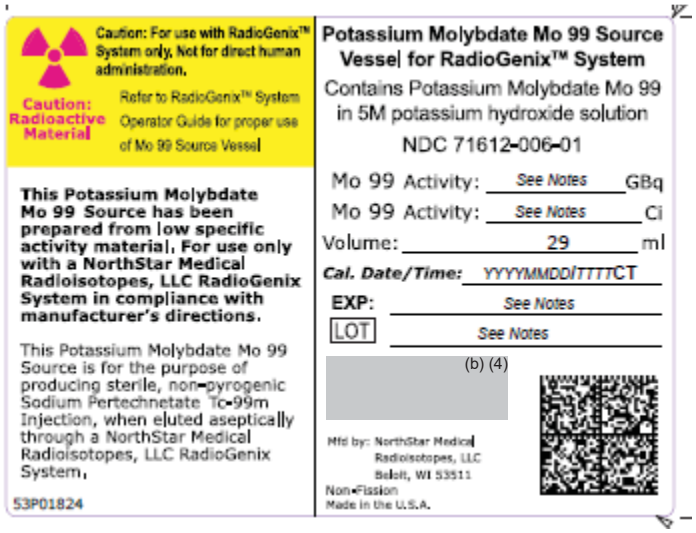
Container labels

Vial Shield

Product Vial



Mo 99 Source



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/s/

IDALIA E RYCHLIK
01/30/2018

HINA S MEHTA
01/30/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs
Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

MEMORANDUM TO FILE: PEDIATRIC REVIEW

From:	Erica Radden, M.D., Medical Officer Division of Pediatric and Maternal Health (DPMH) Office of New Drugs (OND)
Through:	Mona Khurana, M.D., Pediatric Team Leader, John Alexander, M.D., M.P.H., Deputy Director DPMH, OND
To:	Division of Medical Imaging Products (DMIP)
Drug:	RadioGenix System Technetium Tc99m Generator (Sodium Pertechnetate Tc 99m Injection)
Pharmacologic Class:	Radiopharmaceutical agent
Application Number:	NDA 202158
Applicant:	NorthStar Medical Radioisotopes, LLC
Subject:	Pediatric Labeling Review
Proposed Indication:	The RadioGenix System is used to produce Sodium Pertechnetate Tc-99m Injection. Sodium Pertechnetate Tc-99m Injection is for use in the preparation of FDA-approved diagnostic radiopharmaceuticals, as described in the labeling of these diagnostic radiopharmaceutical kits. Sodium Pertechnetate Tc- 99m Injection is also used: In Adults for:

- Thyroid Imaging
- Salivary Gland Imaging
- Urinary Bladder Imaging (direct isotopic cystography) for detection of vesicoureteral reflux
- Nasolacrimal Drainage System Imaging (dacryoscintigraphy)

In Pediatric Patients 0-17 years of age for:

- Thyroid Imaging
- Urinary Bladder Imaging (direct isotopic cystography) for detection of vesicoureteral reflux.

Dosage Form: The RadioGenix System extracts Tc-99m from a molybdate Mo-99 source to produce approximately 5mL Sodium Pertechnetate Injection solution. The solution's strength is determined in the nuclear pharmacy and varies with the radioactivity in the molybdate Mo-99 source.

Route of Administration: Administered by intravenous injection; or instilled into the urinary bladder (for bladder imaging) or eye (for nasolacrimal imaging).

Proposed Dosing Regimen: Dose ranges in the average adult (70kg) are:

Indication	MBq	mCi
Vesico ureteral imaging:	18.5 to 37	0.5 to 1
Thyroid gland imaging:	37 to 370	1 to 10
Salivary gland imaging:	37 to 185	1 to 5
Nasolacrimal drainage system:	3.70 (max)	0.100 (max.)

Dose ranges in pediatric patients 0-17 years of age are:

Indication	**MBq**	**mCi**
Vesico ureteral imaging:	18.5 – 37	0.5 – 1
Thyroid gland imaging:	2.2 – 2.96	60 – 80 µCi per kg

Consult Request:

DMIP consulted DPMH to review the resubmission for this new drug application (NDA) and provide recommendations for pediatric use information in labeling.

Materials Reviewed:

- DPMH Consult request (entered in DARRTS May 15, 2017)
- Applicant's proposed labeling (entered in DARRTS May 8, 2017)
- DPMH's prior review for NDA 202158 (dated October 18, 2013 in DARRTS)
- UltraTechneKow DTE Generator (NDA 017243) labeling dated February 18, 2014 in Drugs@FDA

- TechneLite (NDA 017771) labeling dated February 12, 2014 in Drugs @FDA
- Drytec (NDA 017693) labeling dated August 7, 2015 in Drugs @FDA

I. Regulatory History for this Application

NorthStar Medical Radioisotopes, LLC initially submitted their 505(b)(2) NDA on January 4, 2013 under the name TechneGen Generator System which resulted in a Complete Response on November 4, 2013 due to Chemistry, Manufacturing and Controls (CMC) and Microbiology deficiencies. On May 7, 2017, NorthStar Medical Radioisotopes resubmitted their 505(b)2 application for NDA 202158 under the name RadioGenix System. After resubmission, the applicant lost their original reagent bag manufacturer and submitted a major amendment on October 13, 2017 to include data supporting the use of reagent bags from their new manufacturer.

The RadioGenix System separates the Tc-99m isotope from its parent Mo-99 and produces the radioactive drug Sodium Pertechnetate Tc 99m Injection which, the applicant contends, meets the requirements of its monograph in the USP. This product is submitted as a 505(b)(2) application with reference to FDA's finding of safety and effectiveness for UltraTechneKow DTE Generator (NDA 017243) TechneLite (NDA 017771), and Drytec (NDA 017693) as the reference listed products. These products also produce Sodium Pertechnetate Tc-99m Injection as their final drug product and are currently approved for the same proposed populations, indications and dosing noted above for the RadioGenix System. See DPMH's prior review for NDA 202158 for further background information. Note that UltraTechneKow DTE Generator was originally approved for the additional indications of Brain Imaging, Placenta Localization, and Blood Pool Imaging. However, current labeling does not include those additional indications.

The RadioGenix System will employ a new non-fission process to formulate Sodium Pertechnetate Tc99m Injection solution. However, this product will not provide a new active ingredient, indication, dosage form, dosage regimen or route of administration as compared to the reference listed products; therefore, the Pediatric Research and Equity Act (PREA) is not applicable. Nevertheless, the applicant is seeking approval for pediatric patients 0-17 years of age.

II. DPMH Review of Pediatric Use Labeling

The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population.

For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population. (Also see draft Guidance for Industry and Review Staff, Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling, February, 2013)

This DPMH-Pediatric team labeling review will specifically focus on edits to Subsections 2.2 (Recommended Dose for Pediatric Patients), and 8.4 (Pediatric Use). The following recommendations are based on labeling discussions between DMIP and DPMH. Additions are proposed as underlined text and proposed deletions as strikethroughs in the relevant text.

Applicant's Proposed Labeling

2.2 Recommended Dose for Pediatric Patients

The suggested dose ranges employed for various diagnostic indications in PEDIATRIC PATIENTS are as follows [See *Warnings and Precautions (5.1)* and *Use in* (b) (4) *Specific Populations (8.4)*].

Table 2 Recommended Dosages for PEDIATRIC PATIENTS

Indication	Megabecquerels	Millicuries (mCi)	Administration Technique
Vesico-ureteral imaging:	18.5 – to 37	0.5 – to 1	Intravesicular via a urethral catheter
Thyroid gland imaging:	2.2– to 2.96 per kg (b) (4)	(b) (4) 0.06 to 0.08 per kg (b) (4)	Intravenous

DPMH Comments: These revisions to the applicant's proposed labeling were provided to clarify that the correct title of the section under which subsection 8.4 falls is Use in Specific (b) (4) *Populations. Additionally, the table provides information about maximum dosing and the administration technique to prescribers.*

Applicant's Proposed Labeling

8.4 Pediatric Use

Safety and effectiveness have been established for sodium pertechnetate Tc 99m in pediatric patients from birth to 17 years of age for thyroid imaging and urinary bladder imaging via direct isotopic cystography for the detection of vesico-ureteral reflux based on clinical experience. Although dose adjustment based on body size or weight is generally recommended, the administered dose should be adequate to obtain acceptable quality diagnostic information *[see Dosage and Administration 2.2].* Radiation risks of Sodium Pertechnetate Tc-99m Injection are greater in pediatric patients than adults. *[See*

Warnings and Precautions (5.1)]. Safety and effectiveness have not been established sodium pertechnetate Tc 99m in pediatric patients for salivary gland and nasolacrimal drainage system imaging. (b) (4)

(b) (4)

(b) (4)

DPMH Comments: Labeling should describe the population and indications for which the product is approved in addition to the basis for that approval. Therefore, language was added to describe that use has been established in the entire pediatric population (ages 0-17 years of age) for thyroid and vesico-ureteral imaging. Additionally, the applicant is relying on the findings of safety and effectiveness for these indications from the reference listed product which were based on clinical experience. Furthermore, while the Dosing and Administration section provides a general guide for dosing based on size and weight, the ultimate determination for dosing should use the smallest dose possible to obtain acceptable quality diagnostic information. This subsection should also note safety concerns that are specific to the pediatric population. Accordingly, prescribers are advised that radiation risks are greater in pediatric patients than adults, and referred subsection 5.1 in Warnings and Precautions which provides more detailed information on radiation risks. Labeling should also clarify the adult indications for which the product is not approved in pediatric patients. Therefore, language was also added to describe that safety and effectiveness have not been established in pediatric patients for salivary gland and nasolacrimal drainage system imaging.

III. DPMH Actions and Labeling Recommendations:

DPMH reviewed the applicant's draft labeling and participated in the internal meetings between August 2017 and January 2018. Recommended labeling for the pediatric population based on labeling discussions between DMIP, the Labeling and Development Team, and DPMH is provided per 21 CFR 201.57(c)(9)(iv). DPMH's input will be reflected in the final labeling and the approval letter. Final labeling will be negotiated with the applicant and may not fully reflect changes suggested in this review.

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/s/

ERICA D RADDEN
01/17/2018

MONA K KHURANA
01/18/2018

JOHN J ALEXANDER
01/18/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: January 17, 2018

To: Alberta E. Davis-Warren, Regulatory Project Manager, (DMIP)

Michele Fedowitz, Associate Director for Labeling, (DMIP)

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for RadioGenix System (technetium Tc 99m generator)

NDA: 202158

In response to DMIP consult request dated May 19, 2017, OPDP has reviewed the proposed product labeling (PI) and the Operator Guide for the original NDA submission for RadioGenix System.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DMIP on January 10, 2018, and are provided below.

Operator Guide: OPDP has reviewed the attached proposed Operator Guide received by electronic mail from DMIP on January 10, 2018, and our comments are provided below. Please note that our review was limited to content pertaining to the drug product and we defer to CDRH for the review of non-drug related content.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

161 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

DAVID F FOSS
01/18/2018

Label and Labeling and Human Factors Results Review

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	January 12, 2018
Requesting Office or Division:	Division of Medical Imaging Products
Application Type and Number:	NDA 202158
Product Name and Strength:	RadioGenix System
Product Type:	Combination Product
Rx or OTC:	RX
Applicant/Sponsor Name:	NorthStar Medical Radioisotopes, LLC
Submission Date:	May 8, 2017
OSE RCM #:	2017-1723 and 2017-1426
DMEPA Safety Evaluator:	Idalia E. Rychlik, PharmD.
DMEPA Team Leader:	Hina Mehta, PharmD.
DMEPA Associate Director for Human Factors:	Quynh Nhu Nguyen, MS

1 REASON FOR REVIEW

The Division of Medical Imaging Products (DMIP) requested DMEPA review the Human Factors (HF) Study Results, Prescribing Information (PI) and carton & container labeling for NDA 202158, the RadioGenix System. NorthStar Medical Radioisotopes submitted a response to a Complete Response for RadioGenix System (NDA202158) on May 5, 2017.

1.1 PRODUCT DESCRIPTION

The RadioGenix System is a closed automated system used to process solutions of non-Uranium sourced Potassium Molybdate Mo-99 to produce Sodium Pertechnetate Tc-99m Injection. Sodium Pertechnetate Tc 99m Injection is for use in the preparation of FDA-Approved diagnostic radiopharmaceuticals, as described in the labeling of these diagnostic radiopharmaceutical kits.

Figure 1: RadioGenix System

1.2 REGULATORY HISTORY

On January 4, 2013 NorthStar submitted a 505(b)(2) application for NDA 202158, TechneGen Generator System for Preparation of Sodium Pertechnetate Tc99m Injection. On March 18, 2013 NorthStar received a filing communication from DMIP that contained comments regarding the human factors validation protocol and operator manual and on March 19, 2013 the DMEPA provided comments to NorthStar about the human factors protocol. On November 4, 2013, the application received a Complete Response (CR) for clinical and product quality issues. A type C meeting was held to review the numerous concerns the Agency expressed regarding the human factors approach.[a]

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

[a] Northstar Medical Radioisotopes, LLC. Meeting Preliminary Comments: PIND 109871 RadioGenix System. Type C Meeting. Madison, Wi. NorthStar Medical Radioisotopes, LLC. 2015 Jun 25.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	**Appendix Section (for Methods and Results)**

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine post-market safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the Human Factors (HF) validations study results, supporting documentation (i.e. Operators Guide, RadioGenix User Training Presentation and Instructional Videos), PI, carton and container labeling to determine if the proposed labels, labeling and HF validation study results adequately mitigate medication use errors.

On July 7, 2017, July 14, 2017, August 29, 2017 and September 13, 2017 DMEPA issued Information Requests to further clarify the Human Factors (HF) study results, NorthStar responded on July 13, 2017, August 1, 2017, September 13, 2017 and September 19, 2017 respectively.

CDRH HF team was consulted to review the human factors validation study results; we worked with the CDRH HF team to review the validation study results. CDRH did not identify any concerns with the study results.

3.1 HF Results Assessment

Overall 30 participants (15 nuclear pharmacists and 15 nuclear pharmacy technicians) committed 48 critical errors and 16 close calls while performing tasks associated with the RadioGenix System. NorthStar determined that the current risk controls were effective in mitigating these errors. When the RadioGenix System is obtained by a licensed nuclear pharmacy, all nuclear pharmacists and nuclear pharmacy technicians using the RadioGenix System will complete a training program through NorthStar. The training program is reflective of real use, and is conducted over a six to eight hour period. There are three primary training components for the program.

1. Lecture/presentation on the system operation and videos
2. Hands on training with simulated RadioGenix System
3. Addition hands on practice time for users

RadioGenix System users also have continuous access to the RadioGenix Operator's Guide and step-by-step video tutorials through the computer screen interface that resides on the system. .

During the knowledge probes some participants seemed confused about the difference between the red Stop button and the Stop Protocol button on the interface, which could indicate this is a point that should be better emphasized in training. However, none of the participants utilized the buttons incorrectly during the evaluations, and whenever participants needed to restart a protocol they correctly used the Stop Protocol button rather than the red Stop button which generates a system fault. We agree that all current risk control were effective in mitigating use errors and have no further recommendations as this time. A summary of these errors is provided in tables below:

Table 1. List of tasks failures, root cause analysis and recommendations for Scenario #2 (Add Source Vessel) Errors

Critical Tasks	**# of Errors by User Group**	**Error Description**	**Failure Effects**	**Sponsor Provided Root Cause Analysis**	**Sponsor Proposed Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
Survey the source bay door with wand	Use Errors: 2 Pharmacists	Omits, the pharmacists indicated that they knew that the tasks have to be done but skipped the task during the study. These two participants omitted this step in the other scenarios as well.	Potential for moderate radiation exposure if radioactive material present	Study Artifact	Standard facility procedure Training, Operator Guide, and Instructional videos all clearly outline instructions on performing this task. *Additional suggested mitigation strategies: None*	Task is considered standard practice for nuclear pharmacy and is not specific for the proposed product. The subjective data indicated that the participants omitted the steps due to the artificial study environments. In addition, we confirm the Instructional videos and Operators Guide clearly outline the instructions for this task. We have no additional

						recommendations to further mitigate this risk.
Install manifold on source vessel	Close calls: 1 Pharmacist 2 Technicians	One tech installs manifold crooked; corrects after catheter won't go in. Other tech had difficulty, and removes multiple times and reinstalls. Pharmacist attempts to install without removing black cap. All participants identified and self-corrected the error without any intervention from the study moderator.	Minor delay in task completion	Design allows user to unscrew at incorrect connecti on point.	Training, Operator Guide, and Instructional videos all clearly outline instructions on performing this task. If manifold is not installed correctly user is not able to continue. *Additional suggested mitigation strategies: None.*	The design of the manifold halts the user from continuing if installed incorrectly. We reviewed the Instructional videos and Operators Guide provided, we have no additional recommendations, to further mitigate this risk.

Table 2. List of tasks failures, root cause analysis and recommendations for Scenario #3 (Remove Source Vessel) Errors

Critical Tasks	**# of Use Errors and Close Calls by User Group**	**Error Description**	**Failure Effects**	**Sponsor Provided Root Cause Analysis**	**Sponsor Proposed Mitigation Strategies**	**Recommendations**
Survey the source bay door with wand	Use Errors: 3 Pharmacists	Omit	Potential for moderate radiation exposure if radioactive material present	Study Artifact	Standard facility procedure Training, Operator Guide, and Instructional videos all clearly outline instructions of performing this task. *Additional suggested mitigation strategies: None*	As in the previous scenario, the task is considered standard of practice for nuclear pharmacy. The subjective data was provided by the indicated that the participants omitted the steps due to the artificial study environments.. In addition, we confirm the Instructional videos and Operators Guide clearly outline the instructions for this task. We have no additional recommendations to further mitigate this risk.

Disconnect catheter from bulkhead	Use Errors: 1 Pharmacist	Unscrewed the catheter at the wrong connection point (brown piece) instead of up against the bulkhead. Participant identified and self-corrected the error without any intervention from the study moderator.	Minor delay in task completion and would not result in harm.	Design allows user to unscrew at incorrect connection point.	Training Operator Guide Instructional videos all clearly outline instructions on performing this task. *Additional suggested mitigation strategies: None.*	We confirm the Instructional videos and Operators Guide clearly outline the instructions for this task. Given the participant was able to self-correct during the course of using the product we have no additional recommendations to further mitigate this risk.
Cap catheter with luer cap	Use Errors: 1 Pharmacist	Omits, then sees in video and corrects. Participant identified and corrected the error. Participant stated instruction video integrated as part of the RadioGenix System is clear and the participant simply forgot to do.	Potential for moderate increase in radiation exposure if radioactive material present	User lapse	Training Operator Guide Instructional videos (used by participant to correct error during performance) all clearly outline instructions on	We confirm the Instructional videos and Operators Guide clearly outline the instructions for this task. We have no additional recommendations to further mitigate this risk.

					performing this task. *Additional mitigation strategies: None*	
Cap bulkhead with blue cap	Use Errors: 1 Pharmacist	Drops cap on ground and places on bulkhead; aseptic error.	Potential contaminatio n risk	Study artifact User lapse of standards of practice.	Training Operator Guide *Additional mitigation strategies: None*	We confirm the Instructional videos and Operators Guide clearly outline the instructions for this task. We have no additional recommendations to further mitigate this risk.
Unlock manifold and pull slightly away from vessel	Use Errors: 3 Pharmacists	Two pharmacists unlocked and removed manifold after crimping and cutting the catheter in front of the manifold; additional pharmacist also cut catheter a second time.	Potential for radiation exposure and minor delay in task completion	Unknown. Participants demonstrated understanding of correct action in debriefing.	Training Operator Guide Instruction al videos all clearly outline instruction s on performing this task. *Additional mitigation strategies: None*	The sponsor did not provide a root cause for these errors. However, we confirm the Instructional videos and Operators Guide clearly outline the instructions for this task. We have no additional recommendations to further mitigate this risk.

Install shipping cap and tighten screw	Use Errors: 1 Pharmacist	Omits	Potential contamination risk	Potential study artifact	Training Operator Guide Instructional videos all clearly outline instructions on performing this task. *Additional mitigation strategies: None*	We confirm the Instructional videos and Operators Guide clearly outline the instructions for this task. No subjective data was provided by the Sponsor to determine why participants omitted the steps. We have no additional recommendations to further mitigate this risk.

Table 3. List of task failures, root cause analysis and recommendations for Scenario #4 (Elution) Errors

Critical Task	**# of Use Errors and Close Calls by User Group**	**Error Description**	**Failure Effects**	**Sponsor Provided Root Cause Analysis**	**Sponsor Proposed Mitigation Strategies**	**Recommendations**
Insert TPC into shield and press down	Use Errors: 1 Pharmacist	Tried to insert TPC into shield backwards. TPC would not go in. Applied more force and something	Wasted TPC; delay in task completion	Unknown. Participant demonstrated understanding of correct action	TPC is designed to go into shield only in the correct orientation; design encourages	Product is designed to only insert in the correct orientation. We confirm the Instructional videos and Operators Guide clearly outline the instructions for this task. We have no

		sounded like a snap. Participant turned TPC around and inserted correctly. Then participant said they would not use this TPC because of the sound. Then indicated they would not use the vial because it had now been pierced. Got a new vial and TPC and corrected error. Participant identified and corrected the error.		during debriefing and was able to correct error during the study.	self-correction Training Operator Guide Instructional videos all clearly outline instructions on performing this task. *Additional mitigation strategies: None*	additional recommendations to further mitigate this risk.
Survey product door with wand	Use Errors: 5 Pharmacists	Omit	Potential radiation exposure if radioactive material present	Study artifact For one pharmacist, the moderator had not pointed out that a wand was available in	Standard facility procedure Training Operator Guide Instructional videos Additional suggested mitigation strategies:	As in the previous scenario, task is considered standard of practice for nuclear pharmacy. The subjective data provided by the participants indicated that the participants omitted the steps due to the artificial study environments. In addition, we confirm the Instructional videos and

				the cold scenario room	None	Operators Guide clearly outline the instructions for this task. We have no additional recommendations to further mitigate this risk.
Dispose of port cap as radiological waste	Use Errors: 1 Pharmacist	Disposes of as regular waste.	Potential radiation exposure if radioactive material present	User lapse of nuclear pharmacy practice standards.	Standard facility procedure Training Operator Guide Instructional videos all clearly outline instructions on performing this task. *Additional suggested mitigation strategies: None*	Task is considered standard of practice for nuclear pharmacy. In addition, we confirm the Instructional videos and Operators Guide clearly outline the instructions for this task. We have no additional recommendations to further mitigate this risk.
Wipe product port with (b) (4)	Use Errors: 1 Pharmacist	Omits	Potential contamination	User lapse of nuclear pharmacy practice standards.	Training Operator Guide Instructional videos all clearly outline instructions on performing this task.	We confirm the Instructional videos and Operators Guide clearly outline the instructions for this task. No subjective data was provided by the Sponsor to determine why participants omitted the steps. We have no additional

					Additional suggested mitigation strategies: None	recommendations to further mitigate this risk.
Dispose of wipe as radiological waste	Use Errors: 1 Technician 1 Pharmacist	Technician disposes wipe as regular waste Pharmacist omits after failing to wipe product port (nothing to dispose).	Potential contamination	Study artifact User lapse of nuclear pharmacy practice standards.	Training Operator Guide Instructional videos all clearly outline instructions on performing this task. *Additional suggested mitigation strategies: None*	Task is considered standard of practice for nuclear pharmacy. In addition, we confirm the Instructional videos and Operators Guide clearly outline the instructions for this task. We have no additional recommendations to further mitigate this risk.
Insert shield into product loader	Close calls: 2 Pharmacists	Both pharmacist put shield in backwards a few times, then figured out the problem and inserted correctly.	Minor delay in task completion	Unknown.	Shield designed to go in loader only in the correct orientation; design encourages self-correction Training Operator Guide Instructional videos all clearly outline instructions on performing this	Product designed to only insert in the correct orientation. We confirm the Instructional videos and Operators Guide clearly outline the instructions for this task. We have no additional recommendations to further mitigate this risk.

					task. *Additional suggested mitigation strategies: None*	
Dispose of TPC as radiological waste using tongs	Use Errors: 2 Pharmacists	Doesn't use tongs intentionally.	Negligible increase in radiation exposure	User lapse of nuclear pharmacy practice standards.	Standard best practice Training Operator Guide Instructional videos all clearly outline instructions on performing this task. *Additional suggested mitigation strategies: None*	Task is considered standard of practice for nuclear pharmacy. No subjective data was provided by the Sponsor to determine why participants omitted the steps. In addition, we confirm the Instructional videos and Operators Guide clearly outline the instructions for this task. We have no additional recommendations to further mitigate this risk.
Indicate they would take vial shield to kitting area)	Use Errors: 3 Technicians	When asked, one said vial would then be disposed of as rad waste, the other indicated they would compound with it and one stated it would be stored.	Wasted material; none	Study artifact Semantic discrepancy	Standard facility procedure Training Operator Guide *Additional suggested mitigation strategies: None*	Task is considered standard of practice for nuclear pharmacy. In addition, we confirm the Instructional videos and Operators Guide clearly outline the instructions for this task. We have no additional recommendations to further mitigate this risk.

One additional participant committed an error that did not occur during a critical task. After the elution was complete, the pharmacist

surveyed the product door with the meter as expected. However, the meter detected a level of radiation that was higher than normal and the pharmacist stated that the system was "screaming hot." The pharmacist proceeded to open the product door and observed leakage within the system. They then left the product door open and indicated they needed to find something to wipe up the leakage. Because this was a potentially unsafe situation, the moderator instructed the participant to close the product door before performing any further actions. After closing the product door, the pharmacist continued to try and locate appropriate materials to clean the leakage. The moderator then requested that the session be paused and called NorthStar in to assess the safety of the situation. After the incident, the participant completed the rest of the scenario successfully using another RGX system. Although no other critical errors were committed by this pharmacist during the scenario, the participant was given a "fail" rating because their actions could have caused unnecessary radiation exposure to themselves or others in the lab. During the debriefing, the participant appeared to believe that they followed protocol correctly even though participants were not instructed to open product doors if radiation was detected. The participant's lack of experience with nuclear pharmacy practice during previous years could have contributed to the observed actions. The participant practiced as a nuclear pharmacist until 2007, but had since become a vice president in the company and had not performed an elution since then. The observed performance during this scenario constituted the only failure of the scenario, and the design of the system and training program did not contribute to the error. One other participant experienced a leakage issue but correctly responded to it and completed the protocol successfully.

We note, NorthStar acknowledged that the leaking occurred due to a material failure in the TPC. This failure caused cracking when exposed (b) (4). NorthStar addressed this issue by removing (b) (4) and switched to hydrogen peroxide wipes. They also changed the TPC material from (b) (4), to a (b) (4).

Table 4. List of task failures, root cause analysis and recommendations for Scenario #5 (Install Reagents) Errors

Critical Task	# of Use Errors and Close Calls by User Group	Error Description	Failure Effects	Sponsor Provided Root Cause Analysis	Sponsor Proposed Mitigation Strategies	Recommendations

Remove scrub caps from reagent ports	Close Call: 2 Technicians	Removes saline cap by error; recognizes port must be covered and requests another cap. Both participants identified and corrected their action.	Minor delay in task completion	Proximity of saline cap to scrub caps	Training Operator Guide Instructional videos all clearly outline instructions on performing this task. *Additional suggested mitigation strategies: None*	We confirm the Instructional videos and Operators Guide clearly outline the instructions for this task. We have no additional recommendations to further mitigate this risk.
Survey the PSC door with wand	Use Errors: 3 Pharmacists	Omit	Potential radiation exposure if radioactive material present	Study artifact	Standard facility procedure Training Operator Guide Instructional videos all clearly outline instructions on performing this task.	As in the previous scenario, task is considered standard of practice for nuclear pharmacy. The subjective data provided by the participants indicated that the participants omitted the steps due to the artificial study environments. In addition, we confirm the Instructional videos and Operators Guide clearly outline the instructions for this task. We have no additional recommendations to further mitigate this risk.

Dispose of PSC as rad waste	Use Errors: 1 Pharmacist	Disposed of as chemical waste	Potential radiation exposure if radioactive material present	User lapse of nuclear pharmacy practice standards.	Operator Guide Training Instructional videos *Additional suggested mitigation strategies: None*	Task is considered standard of practice for nuclear pharmacy. In addition, we confirm the Instructional videos and Operators Guide clearly outline the instructions for this task. We have no additional recommendations to further mitigate this risk.
Wipe PSC loaders	Use Errors: 1Pharmacist Close calls: 1 Pharmacist	Omit; one participant recognizes error and corrects.	Potential contamination; Delay in task completion	User lapse of nuclear pharmacy practice standards.	Operator Guide Training Instructional videos all clearly outline instructions on performing this task. *Additional suggested mitigation strategies: None*	We confirm the Instructional videos and Operators Guide clearly outline the instructions for this task. No subjective data was provided by the Sponsor to determine why participants omitted the steps. We have no additional recommendations to further mitigate this risk.
Dispose of wipes as radiological waste	Use Errors: 2 Pharmacists	One pharmacist disposed of as chemical waste and the other disposed as regular waste	Potential radiation exposure if radioactive material present	User lapse of nuclear pharmacy practice standards.	Standard facility procedure Training Operator Guide Instructional videos all clearly outline instructions on performing this task. *Additional suggested mitigation strategies: None*	Task is considered standard of practice for nuclear pharmacy. In addition, we confirm the Instructional videos and Operators Guide clearly outline the instructions for this task. We have no additional recommendations to further mitigate this risk.

Of note, several participants experienced problems related to mismatching Radio-frequency identification (RFID) tags and incorrectly assembled reagent kits during protocol completion, but all addressed the problems appropriately and successfully completed the protocol. Per IR response from the Applicant, the reagent kit RFID issues were caused by the RFID tags not being properly programmed and packaged during the manufacturing process. In order for the kits to work properly, the RFID for both the PSC and the reagent kits have to match. Without a match the user will get an error. None of the users had an issue with the assembly of the reagent kits and the errors observed with RFID tags were not due to user error.

Table 5. List of task failures, root cause analysis and recommendations for Scenario #6 (Exchange DMC) Errors

Critical Task	# of Use Errors and Close Calls by User Group	Error Description	Failure Effect	Sponsor Provided Root Cause Analysis	Sponsor Proposed Mitigation Strategies	Recommendations
Survey discarded materials door with wand	Use Errors: 1 Technician	Surveyed door #2 instead of door #1, then surveyed correct door Participant identified and self-corrected the error	Minor delay in task completion	User lapse of nuclear pharmacy practice standards.	Standard facility procedure Training Operator Guide Instructional videos all clearly outline instructions on performing this task. *Additional suggested mitigation strategies: None*	Task is considered standard of practice for nuclear pharmacy. In addition, we confirm the Instructional videos and Operators Guide clearly outline the instructions for this task. We have no additional recommendations to further mitigate this risk.

Survey reagents door with wand	Use Errors: 3 Pharmacists	Omit	Potential radiation exposure if radioactive material present	User lapse of nuclear pharmacy practice standards.	Standard facility procedure Training Operator Guide Instructional videos all clearly outline instructions on performing this task. *Additional suggested mitigation strategies: None*	Task is considered standard of practice for nuclear pharmacy. No subjective data was provided by the Sponsor to determine why participants omitted the steps. In addition, we confirm the Instructional videos and Operators Guide clearly outline the instructions for this task. We have no additional recommendations to further mitigate this risk.
Disconnect container from bulkhead	Close calls: 2 Technicians 2 Pharmacists	One technician disconnected the line from the bulkhead and let line hang from container while tried to install cap on bulkhead connection instead of line. When it did not work, reattached line to bulkhead, then disconnected from container and capped the line. The	Delay in task completion	Unknown.	Cap does not fit on bulkhead connection. Training Operator Guide Instructional videos (used by participant to correct error during performance) all clearly outline instructions	We confirm the Instructional videos and Operators Guide clearly outline the instructions for this task. We have no additional recommendations to further mitigate this risk.

		other technician struggles to disconnect container; asks for a pliers and eventually disconnects without causing damage. Both pharmacists disconnected tube from bulkhead rather than tube from container. Realized cap would not fit on bulkhead, then reattached tube to bulkhead and disconnecting tube from container. All participants identified and corrected the error.			on performing this task. *Additional suggested mitigation strategies: None*	

Table 6. List of task failures, root cause analysis and recommendations for Scenario #7 (Sterilization) Errors

Critical Task	**# of Use Errors and Close Calls by User Group**	**Error Description**	**Failure Effects**	**Sponsor Provided Root Cause Analysis**	**Sponsor Proposed Mitigation Strategies**	**Recommendations**

Survey PSC door with wand	Use Errors: 1 Pharmacist	Opens system door slightly, then closes and surveys Participant identified and corrected the error	potential radiation exposure	User lapse of nuclear pharmacy practice standards.	Standard facility procedure Training Operator Guide Instructional videos all clearly outline instructions on performing this task. *Additional suggested mitigation strategies: None*	Task is considered standard of practice for nuclear pharmacy. In addition, we confirm the Instructional videos and Operators Guide clearly outline the instructions for this task. We have no additional recommendations to further mitigate this risk.
Install air filter	Use Errors: 1 Pharmacist	Installs on top of previous air filter instead of removing the used air filter;	Slight increase in resistance when air pulled into the system; none.	Design of air filters allow them to be attached to one another	Training Operator Guide Instructional videos *Additional suggested mitigation strategies: None. The air filters are a standardized, off-the-shelf component for which design cannot be modified.*	Discussion with micro determined that two filters do not pose an increased sterility risk. We do not have any recommendations to further mitigate the risk for these errors and

Engage PSC loaders	Close calls: 1 Pharmacist	Omits; Participant debriefing states the participant omitted wiping the PSC, recalled it was necessary, removed the PSC, swabbed and completed.	Delay in task completion	Unknown.	Training Operator Guide Instructional videos all clearly outline instructions on performing this task. *Additional suggested mitigation strategies: None*	We confirm the Instructional videos and Operators Guide clearly outline the instructions for this task. We have no additional recommendations to further mitigate this risk.
Insert blank TPC into shield and press down	Close calls: 1 Technician	Inserts backwards; corrects and reinserts.	Minor delay in task completion	Potential study artifact.	TPC designed to go in shield only in the correct orientation; design encourages self-correction Training Operator Guide Instructional videos all clearly outline instructions on performing this task. *Additional suggested mitigation strategies: None*	Product design encourages correct insertion. We confirm the Instructional videos and Operators Guide clearly outline the instructions for this task. We have no additional recommendations to further mitigate this risk.

Survey the product door with wand	Use Errors: 3 Pharmacists	Omit step.	potential radiation exposure	User lapse of nuclear pharmacy practice standards.	Standard facility procedure Training Operator Guide Instructional videos all clearly outline instructions on performing this task. *Additional suggested mitigation strategies: Although utilizing a survey meter during training may help remind some users to perform this task, meters will not likely be available in all instances and would not function in a realistic manner*	As in the previous scenario, task is considered standard of practice for nuclear pharmacy. The subjective data provided by the participants indicated that the participants omitted the steps due to the artificial study environments.. In addition, we confirm the Instructional videos and Operators Guide clearly outline the instructions for this task. We have no additional recommendations to further mitigate this risk.
Insert shield assembly	Close calls: 1 Technician 1 Pharmacist	Both participants insert backwards; correct and reinsert. Participants identified and corrected the error.	Minor delay in task completion	Unknown.	Shield designed to go in loader only in the correct orientation; design encourages self-	Product design encourages correct assembly. We confirm the Instructional videos and Operators Guide

					correction Training Operator Guide Instructional videos all clearly outline instructions on performing this task. *Additional suggested mitigation strategies: None*	clearly outline the instructions for this task. We have no additional recommendations to further mitigate this risk.
Software: Select Continue	Use Errors: 3 Pharmacists	One participant pressed Continue too early before completing steps. System caught the error because it could not detect the TPC. One participant presses Continue before inserting vial shield/TPC. Gets message that says TPC not installed. Presses "Retry" multiple times without correcting the error. Then presses "Abort Protocol" and starts protocol over again.	Delay in task completion	Unknown. Participants stated instruction materials are clear.	System mitigates any failure effects from pressing the button before inserting the TPC by requiring the TPC to be in place before protocol will continue Training Operator Guide Instructional videos all clearly outline instructions on performing this task. *Additional suggested*	The system requires the TPC to be in place correctly prior to continuing with protocol. We confirm the Instructional videos and Operators Guide clearly outline the instructions for this task. We have no additional recommendations to further mitigate this risk.

		Presses Continue through all prompts without redoing then inserts TPC when prompted. Sterilization continues without issues. Another participant removed the reagent module before pressing Continue.			*mitigation strategies: None*	
Clean ozone tubing connectors with scrub caps	Use Errors: 1 Pharmacist	Omits step	Potential contamination introduced into the system	Unknown. Participant states instruction video is clear.	Inclusion of scrub caps in each procedure kit Training Operator Guide Instructional videos all clearly outline instructions on performing this task. *Additional suggested mitigation strategies: None*	We confirm the Instructional videos and Operators Guide clearly outline the instructions for this task. No subjective data was provided by the Sponsor to determine why participants omitted the steps. We have no additional recommendations to further mitigate this risk.

Place scrub caps on reagent and saline ports	Use Errors: 1 Pharmacist	Omits step.	Potential contamination introduced into the system	Unknown. Participant states instruction video is clear.	Inclusion of scrub caps in each procedure kit Training Operator Guide Instructional videos all clearly outline instructions on performing this task. *Additional suggested mitigation strategies: None*	We confirm the Instructional videos and Operators Guide clearly outline the instructions for this task. No subjective data was provided by the Sponsor to determine why participants omitted the steps. We have no additional recommendations to further mitigate this risk.
Dispose TPC as rad waste with tongs	Use Errors: 3 Pharmacists	Does not use tongs.	Potential radiation exposure	User lapse of nuclear pharmacy practice standards.	Standard best practice Training Operator Guide Instructional videos all clearly outline instructions on performing this task. *Additional suggested mitigation strategies: None*	Task is considered standard of practice for nuclear pharmacy. No subjective data was provided by the Sponsor to determine why participants omitted the steps. In addition, we confirm the Instructional videos and Operators Guide clearly outline the instructions for this task. We have no

						additional recommendations to further mitigate this risk.

3.2 PI, Carton and Container Labeling Assessment

The proposed PI, Carton and Container labels can be improved to increase readability and prominence of important information to promote the safe use of the RadioGenix System and its constituents. The Dosage and Administration section of the PI contains repetitive information and detailed RadioGenix System use information. We advise minimizing content to a broad outline of system use and referencing the user to the appropriate RadioGenix System Operator's Guide to ensure the PI is not used in the place of the Operator's Guide and/or as a manual for operation. The carton and container label need to reflect the correct product name, RadioGenix System.

4 CONCLUSION & RECOMMENDATIONS

The HF validation study results and supporting documentation are found acceptable. Taking standards of nuclear pharmacy practice into consideration and our analysis of the Operator's Guide, Instructional videos and training outlined by NorthStar, examination of the root cause of errors, as well as, participant responses, confirms reasonable expectation that licensed nuclear pharmacy providers should be able to use the RadioGenix System in a safe and effective manner. We have no further recommendations pertaining to HF at this time.

We find the Operator's Guide, RadioGenix User Training presentation and videos acceptable from a medication error perspective and have no further recommendations at this time.

We provide recommendations to address deficiencies in the PI and carton and container labeling in Section 4.1 for the Division and in Section 4.2 for the Applicant.

4.1 RECOMMENDATIONS FOR THE DIVISION

I. PRESCRIBING INFORMATION

i. To avoid a ten-fold misinterpretation of dose, as referenced in ISMP's List of Error-Prone Abbreviations, Symbols and Dose Designations, remove all trailing zeros (e.g. 1.0 mCi) throughout PI. Furthermore, replace all dangerous abbreviation and spell out intended meaning (e.g. µ).

ii. As currently presented, the PI contains extensive information on elution and maintenance instructions. To avoid user reliance on the PI as an operator's guide consider limiting instructions for elution and maintenance of the Radiogenix System from Section 2: Dosage and Administration.

iii. Consolidate basic system scheduled maintenance information into table format.

iv. Product information in Section 16.1: How Supplied should include complete product strengths and appropriate information to facilitate identification of product (e.g. corresponding National Drug Code) for each item.

4.2 RECOMMENDATIONS FOR NORTHSTAR MEDICAL RADIOISOTOPE, LLC

We recommend the following be implemented prior to approval of this NDA 202158:

i. Ensure the approved product name, RadioGenix System is present, readable and legible on labels. Take into account all pertinent factors, including typography, layout, contrast and printing features.
   - To improve readability increase prominence of product information increase the font size of Mo-99 on the source product label

ii. The "Rx Only" statement is required on drug labels by Section 503(b)(4)(A) of the Federal Food, Drug and Cosmetic Act. Therefore, include the statement on all technetium product vial labels, ensuring that it does not compete in prominence with other more important information on the label.

iii. We note that the use of graphics and symbols to convey important product information can be misinterpreted. Therefore, we recommend removing all graphics and symbols and write out all important information as space permits. For example, remove the (b) (4) symbol and insert "EXP" for expiration information, remove the (b) (4) and state the storage information, etc.

iv. The drug barcode is often used as an additional verification during drug selection and prior to drug administration; therefore it is an important safety feature that should be part of the label. We request you add the product barcode to the vial label as required per 21 CFR 201.25(c)(2). Ensure the barcode is surrounded by enough white space to allow scanners to read the barcode properly in accordance with 21CFR201.25(c)(1)(i). Additionally, ensure the barcode is oriented in a scan-able position on the vial label. Barcodes placed in a horizontal position may not scan due to vial curvature.

v. We note that the source vessel label does not include an National Drug Code (NDC) number; therefore, include the NDC number on the top third of PDP or as part of and contiguous to any barcode. Ensure the NDC package code is different between sizes and strengths.

vi. To ensure adequate space for the above required information, we recommend decreasing the font size of the manufacturer information and logo.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for RadioGenix System that NorthStar Medical Radioisotopes, LLC submitted on July 27, 2017, the Source Product and Eluate Product.

Table 2. Product Information for RadioGenix System, , Source Product and Eluate Product			
Product Name	**RadioGenix System**	**Mo-99 Source**	**Extracted Tc-99m**
Initial Approval Date	N/A	N/A	N/A
Active Ingredient	N/A	Molybdate (Mo-99)	Sodium Pertechnetate (Tc-99m)
Indication	The RadioGenix System is a closed automated system used to process solutions of non-Uranium sourced potassium molybdate Mo-99 to produce Sodium Pertechnetate Tc-99m Injection. Sodium Pertechnetate Tc-99m Injection is for use in the preparation of FDA-approved diagnostic radiopharaceuticals, as described in the labeling of these diagnostic radiopharmaceutical kits.	N/A	N/A
Route of Administration	N/A		Intravenous, intraocular, bladder instillation
Dosage Form	N/A	Solution	Solution
Strength	N/A	222 GBq (6 Ci)	varies with the radioactivity of the source material

<table>
<tr><td>Dose Volume Limits</td><td colspan="2">N/A</td><td>Dose ranges in the average ADULT PATIENT (70 kg) are:
<table>
<tr><td>Indication</td><td>MBq</td><td>mCi</td></tr>
<tr><td>Vesico ureteral</td><td>18.5 -37</td><td>0.5-1</td></tr>
<tr><td>Thyroid gland</td><td>37- 370</td><td>1- 10</td></tr>
<tr><td>Salivary gland</td><td>37-185</td><td>1 - 5</td></tr>
<tr><td>Nasolacrimal</td><td>3.7(max)</td><td>0.1</td></tr>
</table>
Dose ranges in PEDIATRIC PATIENTS are:
<table>
<tr><td>Indication</td><td>MBq</td><td>mCi</td></tr>
<tr><td>Vesico ureteral</td><td>18.5- 37</td><td>0.5 – 1</td></tr>
<tr><td>Thyroid gland</td><td>2.2 – 2.96</td><td>60–80 µCi</td></tr>
</table></td></tr>
<tr><td>How Supplied</td><td></td><td>supplied in quantities of 6 Ci at the referenced calibration date and time specified on the source vessel label.</td><td>N/A</td></tr>
<tr><td>Storage</td><td>N/A</td><td colspan="2">20° to 25°C (68° to 77°F)</td></tr>
<tr><td>Container Closure</td><td>N/A</td><td>source vessel constructed of tungsten and depleted uranium to attenuate the radioactivity. The source vessel completely encases a vial.</td><td>Sterile sealed vial encased in a tungsten and depleted uranium vessel to attenuate the radioactivity</td></tr>
</table>

Table 2.1 Presents relevant product information for the Reference Listed Product, NDA017243, Ulta-TechneKow DTE, the Source Product and Eluate Product.

Table 2.1 Product Information for Ultra-Technikow DTE , Source Product and Eluate Product			
Product Name	**Ultra-TechneKow DTE**	**Mo-99 Source**	**Extracted Tc-99m**
Initial Approval Date	N/A	N/A	N/A
Active Ingredient	N/A	Molybdate (Mo-99)	Sodium Pertechnetate (Tc-99m)
Indication	closed automated system used to process solutions of non-Uranium sourced potassium molybdate Mo-99 to produce Sodium Pertechnetate Tc-99m Injection. Sodium Pertechnetate Tc-99m Injection is for use in the preparation of FDA-approved diagnostic radiopharaceuticals, as described in the labeling of these diagnostic radiopharmaceutical kits.	N/A	N/A
Route of Administration	N/A		Intravenous, intraocular, bladder instillation
Dosage Form	N/A	Solution	Solution
Strength	N/A	1 Ci, 1.5 Ci, 2 Ci, 2.5 Ci, 3 Ci, 3.5 Ci, (b) (4) 5 Ci, (b) (4) Ci, 6 Ci, (b) (4) 7.5 Ci, 11 Ci, 14Ci, 16Ci	varies with the radioactivity of the source material
Dose Volume Limits	N/A		Dose ranges in the average ADULT PATIENT (70 kg) are: Indication / MBq / mCi Vesico ureteral / 18.5 -37 / 0.5-1

<table>
<tr><td></td><td></td><td colspan="2"></td><td>
<table>
<tr><td>Thyroid gland</td><td>37- 370</td><td>1- 10</td></tr>
<tr><td>Salivary gland</td><td>37-185</td><td>1 - 5</td></tr>
<tr><td>Nasolacrimal</td><td>3.7(max)</td><td>0.1</td></tr>
</table>
Dose ranges in PEDIATRIC PATIENTS are:
<table>
<tr><th>Indication</th><th>MBq</th><th>mCi</th></tr>
<tr><td>Vesico ureteral</td><td>18.5- 37</td><td>0.5 – 1</td></tr>
<tr><td>Thyroid gland</td><td>2.2 – 2.96</td><td>60–80 µCi</td></tr>
</table>
</td></tr>
<tr><td>How Supplied</td><td></td><td colspan="2">supplied in quantities of (b) (4) at the referenced calibration date and time specified on the source vessel label.</td><td>N/A</td></tr>
<tr><td>Storage</td><td>N/A</td><td colspan="3">20° to 25°C (68° to 77°F)</td></tr>
<tr><td>Container Closure</td><td>N/A</td><td>source vessel constructed of tungsten and depleted uranium to attenuate the radioactivity. The source vessel completely encases a vial.</td><td colspan="2">Sterile sealed vial encased in a tungsten and depleted uranium vessel to attenuate the radioactivity</td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 25, 2017 we searched DMEPA's previous reviews using the terms, Radiogenix System and TechneGen System.

Our search identified 0 previous reviews.

APPENDIX C. HUMAN FACTORS STUDY

C.1 Study Design

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APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following RadioGenix System labels and labeling submitted by NorthStar Medical Radioisotopes, LLC on July 27, 2017.

- Source Product and Vessel label
- Transfer Vessel and Discard Vessel Labels
- Human Factors Validation Study Results (Image not shown)
- RadioGenix User Training (Image not shown)
- Prescribing Information
- Operator's Guide

G.2 Label and Labeling

- Prescribing Information
  \\cdsesub1\evsprod\nda202158\0020\m1\us\114-labeling\114a-draft-label\pi-90q03078.docx

- Operator's Guide
  \\cdsesub1\evsprod\nda202158\0020\m1\us\114-labeling\114a-draft-label\94s05058-system-operator-guide.pdf

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Source Vessel Label

Source Product Label

Transfer Vessel Label

Discard Material Vessel Label

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/s/

IDALIA E RYCHLIK
01/12/2018

HINA S MEHTA
01/12/2018

QUYNHNHU T NGUYEN
01/12/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

Date: October 11, 2013

From: Erica Radden, M.D.
Pediatric and Maternal Health Staff, Office of New Drugs

Through: Hari Cheryl Sachs, M.D., Team Leader
Pediatric and Maternal Health Staff, Office of New Drugs

Jeanine Best, MSN, RN, PNP, Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff, Office of New Drugs

Lynne Yao, M.D., OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

To: Division of Medical Imaging Products (DMIP)

Drug: TechneGen Generator System (sodium pertechnetate Tc99m injection)

Application Number: NDA 202158

Sponsor: NorthStar Medical Radioisotopes, LLC

Proposed Indication: Brain imaging (including cerebral radionuclide angiography, Thyroid imaging, salivary gland imaging, blood pool imaging (including radionuclide angiography), urinary bladder imaging (direct isotopic cystography) for detection of vesico-ureteral reflux, nasolacrimal draining system imaging. Sodium pertechnetate Tc 99m injection is also used to reconstitute a variety of reagent kits, commonly referred to as Technetium Tc99m kits, with each

reconstituted kit used for specified diagnostic imaging indication.

Proposed Dosage form and Route of Administration: Injection of (b) (4). Sodium Pertechnetate Tc 99m is usually administered by intravenous injection, but can be given orally or by direct instillation.

Proposed Dosing Regimen: The dosage employed varies with each diagnostic procedure. If the oral route is elected, the patient should fast for at least six (6) hours before and two (2) hours after administration.

Consult Request:
DMIP consulted the Pediatric and Maternal Health Staff (PMHS) to review the package insert, specifically sections 8.1 Pregnancy, 8.3 Nursing Mothers, and 8.4 Pediatric Use.

Background:
On January 4, 2013, a new 505(b)(2) NDA was submitted for the TechneGen Generator System with the proposed indications for multiple imaging procedures listed above. UltraTechneKow DTE Generator (NDA 017243) is the reference listed product and is approved for the same proposed indications noted above for TechneGen Generator system. However, for UltraTechneKow DTE Generator, although all the indications are applicable to adults, the indications of salivary gland and nasolacrimal draining system imaging are excluded for pediatric patients. This application does not appear to separate adult and pediatric indications.

Reviewer comment: The pediatric and adult indications should be clearly delineated for TechneGen Generator System labeling.

TechneGen Generator System is a device that produces Sodium Pertechnetate Tc99m Injection solution using Potassium Molybdate Mo99 Solution via a non-fission process whereas current production uses Mo99 purified from uranium-235 (U-235) fission product. However, a USA initiative to decrease the distribution and use of this weapons grade U-235 material has been instituted. Additionally, the sponsor claims that there were episodes of severe shortages of fission Mo99 and Tc99m in the last two years to such an extent that diagnostic nuclear medicine imaging procedures were not performed which they have attributed to maintenance and systems failures of the aging nuclear reactors used for the fission-produced Mo99.

The sponsor proposes to include all FDA approved pediatric indications and prescribing information of the reference listed product (UltraTechneKow DTE Generator, NDA 017243) including dose requirements, and asserts that no additional measures are needed to satisfy pediatric requirements. Therefore, the sponsor has not included a request for a waiver, deferral or a protocol for pediatric studies.

Reviewer comment: Although TechneGen Generator System will employ a new non-fission process to formulate Sodium Pertechnetate Tc99m Injection solution, this product will not provide a new active ingredient. In addition, the sponsor's plans to use the same indications and dosing requirements as the reference listed product will not provide a new indication, new dosage form, new dosage regimen or new route of administration. Therefore, the Pediatric Research and Equity Act (PREA) is not triggered.

DMIP requested PMHS' review of pregnancy, nursing mothers and pediatrics use labeling. DMIP plans to issue a Complete Response for TechneGen Generator System due to Chemistry, Manufacturing and Controls (CMC) and Microbiology deficiencies. Labeling has not been discussed this review cycle, and PMHS defers pregnancy, nursing mothers, and pediatric use labeling recommendations and revisions until a future review cycle. PMHS reviewed the proposed package insert, and background information regarding the NDA, and participated in the internal meetings between January, 2013 and June, 2013.

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/s/

ERICA D RADDEN
10/18/2013

JEANINE A BEST
10/18/2013

HARI C SACHS
10/18/2013

LYNNE P YAO
10/19/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

FDA

CONSULT REVIEW MEMORANDUM

To: Ravindra Kasliwal, Lead Reviewer
CDER/OPS/ONDQA/DNDQAIII/BRVII

From: Prasanna Hariharan, PhD, Mechanical Engineer, CDRH/OSEL/DSFM
Matthew R Myers, PhD, Research Physicist, CDRH/OSEL/DSFM

Date: September 24, 2013

Subject: NDA 202158: Review of flow **aspects of the TechneGen™ generator system** for preparation of sodium pertechnetate Tc99m injection

Background/Overview:

Northstar LLC submitted the New Drug Application (NDA) for the TechneGen generator system to produce short-lived radioactive technetium (TC-99m) from longer lived radioactive Molybdenum (Mo-99) solution. The final TC-99m product will be used as a radiopharmaceutical agent for diagnostic imaging procedures. The system uses a resin filter to separate TC-99m from the parent Mo-99 (which has traces of TC-99m). Subsequently, the retained technetium gets washed from the filter using saline solution. The equipment is a "flow-based system" with a micro-processor controlled flow-loop (Figure 1) to transport the parent and daughter fluids, and the cleaning agents. **We reviewed the fluid flow aspects of the TechneGen system and identified deficiencies (listed in the next section) that can potentially affect the safety and effectiveness of the device.** CDRH's concerns were communicated with the applicant during the teleconference held on May 22nd, 2013. The Agency is still waiting for the sponsor's response

(b) (4)

Reviewer comments:

1. Lack of flow or pressure sensors: The flow circuit in the system is very complicated with same tubing lines used multiple times for transporting the source solution, cleaning agents, and the final Tc99 product (Figure 1). Any leaks/blockage in the fluid lines could adversely impact the safety and efficacy of the instrument. Consequently, constant monitoring of the flow circuit is critical to avoid any fluid leaks and to ensure proper functioning of the valves. After reviewing the NDA submission, it was not clear if the TechneGen instrument hosts any sensors to measure flow or pressure in the fluid lines. In pages 141 (4.12) and 162 (4.2.17) of the Drug Master File (DMF 26592), the sponsors had stated that " (b) (4)

(b) (4) However, it was not clear if the radiation sensor has the capability to measure the parent or daughter fluid's flow rate. During the teleconference with FDA (held on May 22, 2013), the applicant clarified that the sensor monitors only the radiation activity and that if the radiation conditions were altered, the system will has (or will have) the capability to shut down or alerts an operator. The applicant explained in detail the system's monitoring and sensor process. The Agency stated that the process sounds like a decision tree and requested the applicant to submit a decision tree that describes the steps in detail. The Agency is awaiting the applicant's response.

During the same teleconference, the sponsors also acknowledged that the system will not host any pressure sensor to detect leaks in the system. In page 741, as a part of hazard analysis, the sponsors have listed solution leak due to tubing/connector failure as a potential safety risk. Consequently, the agency has requested the sponsor to provide proper justification for not using a pressure sensor which could mitigate this safety risk. In addition, the Agency has requested the applicant to provide details about training the users to perform leaks tests prior to loading the radioactive fluids.

2. Kinking of tubes: One of the major safety/efficacy concerns during the operation of the TechneGen instrument is the possibility of partial or complete occlusion of flow lines due to kinking of tubes. This risk is very relevant for tubing lines that are exposed outside the instrument (Figure 2). When the sponsors came to the FDA to demonstrate their device, the FDA reviewers got a chance to check the type of tubing used for the fluid lines and found them to be susceptible to kinks. Fully or partially occluded tubing could adversely affect the quality of the final product and pose safety risk to the operator. To mitigate this risk, the sponsors are proposing to (b) (4) shown in Figure 2). The sponsors claim that the (b) (4) will minimize/eliminate the risk of kinking. We have requested the sponsor to provide evidence that the kinking problem disappeared after (b) (4)

It should also be noted that the sponsors are not proposing to (b) (4) tubing inside the instrument (Figure 1). Since the same type of tubing is used inside the device, kinking could still be a potential long-term issue. Consequently, we have requested Northstar to deliberately kink the tubing at key locations (such as near valves and connectors), and observe if the product quality is affected due to the reduction in the flow rate. **The Agency is awaiting the applicant's response.**

3. Effect of fluid flow rate: The Agency has requested Northstar to provide measurements of product quality over a wider range of flow rates. Presently only the design and two times the design flow rates have been tested. After evaluating the results from this study, the sponsors have stated that the product yield does not change even after doubling the flow rates. For the low-flow scenario, the sponsors have stated (in page 777 of the submission as a part of safety margin testing) that "***a slower flow rate does not adversely affect the performance of the final product. It may actually provide a slight improvement in the product yield***". However, it is not clear how a slower flow rate would help in

improving the product yield. Consequently, we have requested the company to provide proper scientific justification for this statement.

4. Effect of malfunctioning valves: Another potential safety hazard for this device is the failure of the valves to open or shut as instructed by the firmware while the syringe pump continues to operate. This could cause an increase in pressure in fluid lines which can eventually lead to leakage of radioactive fluids. Malfunctioning valves could also adversely affect the elution efficacy and reduce the quality of the final product. Consequently, we have requested the company to simulate the effect of malfunctioning valves by replacing valve with open tube (valve fails open) or clamping the tube next to the valve (valve fails closed). We are awaiting the applicant's response.

5. Potential for incomplete cleaning. In order that we can better assess the role of flow features on the cleaning efficacy, the manufacturer should provide the flow rate (minimum, maximum, and average) flow rate through each valve and filter. The engineering drawings for each type of valve should also be submitted.

Summary of Requests of Manufacturer

Most of the following requests have been made of the manufacturer, but it may be wise to repeat them at the present time.

1. Please install pressure sensors within the flow loop, or justify why such sensors are not necessary. Include in your justification scenarios where a valve may close shut or a tube may kink, causing pressure to rise.

2. Please describe measures taken to reduce the likelihood of kinks, both external and internal to the instrument.

3. Please perform experiments where you occlude the tubing to simulate a kinked tube or valve failed close. Please provide pressure measurements and observations of system response. The duration of observation should be long enough that the steady-state response of the system occurs, e.g. that which would occur if no one was available to immediately intervene.

4. Please provide measures of product quality over a wider range of flow rates than the factor of two already investigated. Provide the range of flow for which product quality is acceptable.

5. Please provide the minimum, maximum, and average flow rate likely to occur through all valves and membranes. Please also provide engineering drawings for each type of valve.

Prasanna Hariharan
2013.09.24 14:57:27 -04'00'

Prasanna Hariharan

MEMO OF

SOFTWARE REVIEW

of a MODERATE Level Of Concern device

NDA: 202158

DATE: 9/24/13

FROM:	Joseph Jorgens III, Senior Biomedical and Software Engineer		OSEL-DESE	301-796-2588
TO:	Ravi Kasliwal	CDER/OPS/ONDQA	WO21 1606	301-796-1386
TO:	Alberta Davis-Warren	CDER/OND/ODEIV/DMIP	WO22 2358	301-796-3908

SUBJECT: Software review of the NorthStar Medical Radioisotopes' TechneGen Instrument. NorthStar 5249 Femrite Road, Madison Wi. Contact: Scott Moffatt VP of RA/QA 608-230-7163.

Succinct Conclusion: ADDITIONAL INFORMATION REQUIRED

The information provided in this submission is insufficient to meet the software concerns as described in the Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices, and it is recommended that, from a software standpoint, additional information be acquired in order to complete the review of this submission.

SUMMARY:

Northstar LLC submitted the New Drug Application (NDA) for the TechneGen generator system to produce short-lived radioactive technetium (TC-99m) from longer lived radioactive Molybdenum (Mo-99) solution. The final TC-99m product is used as a radiopharmaceutical agent for diagnostic imaging procedures. The system uses a resin filter to separate TC-99m from the parent Mo-99 (which has traces of TC-99m). Subsequently, the retained technetium gets washed from the filter using saline solution. The equipment is a "flow-based system" with a micro-processor controlled flow-loop to transport the parent and daughter fluids, and the cleaning agents.

The TechneGen is the equipment part of the TechneGen Generator System (TGS) instrument used to produce Tc99m for use as a sodium pertechnetate, Tc99m imaging agent and for preparation of a number of Tc99m labeled radiopharmaceutical agents used in diagnostic imaging procedures. The TGS receives Mo99 that is produced by a nuclear reactor or linear accelerator and converts it into concentrated sodium pertechnetate, Tc99m injection, suitable for preparing Tc99m labeled diagnostic imaging agents for a variety of diagnostic imaging procedures.

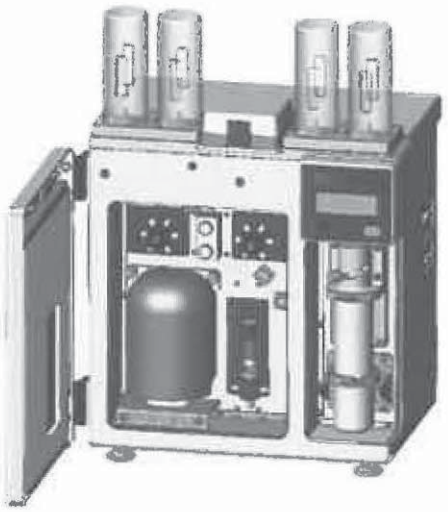
The TechneGen Generator System is a microprocessor-controlled instrument for use by a radioactive material (RAM) authorized practitioner and/or trained nuclear pharmacist, This chemical separation system may be used to quickly and efficiently prepare a high purity daughter radioisotope of suitable chemical and pharmaceutical quality for use in diagnostic imaging procedures or to prepare radiotherapy agents. The TechneGen Generator System has been specifically designed to process sodium pertechnetate Tc99m and facilitates the purification and handling of the parent-daughter radioisotope pair Mo99 /Tc99m to produce a high purity solution of sodium pertechnetate Tc99m Injection USP. The TechneGen Generator System has been uniquely developed to efficiently, routinely, and reproducibly separate high purity short-lived Tc99m from its longer lived parent, Mo99.

The TechneGen Generator System consists of three major physical components.

The first component is the host computer running the custom application software using the Microsoft .NET architecture.

The second is the instrument itself which houses an assortment of pumps, valves, fluid lines, radiation shielding, sensors, indicators and control electronics.

The third component is the chemistry reagents and separation cartridges that are designed specifically to coordinate the required sequences and methods for isotopic separation.



Software Controlled Aspects of the Device

All components of the device are controlled/monitored by software, which is responsible for the functionality, user interface, safety checks and performance accuracy.

SOFTWARE REVIEW

1. **Level Of Concern: Not Acceptable**
The firm did not provide the Level Of Concern and the supporting rationale. It speaking with Phillip Davis and Jessica Cole on 9/10/13 it was concluded that the Level Of Concern should be MODERATE. This should be provided.

2. **Software Description: Not Acceptable**
The firm did not provide in a separate Section a comprehensive overview of the device features that are controlled by software, and a description of the intended operational environment, which would include information on the programming language, the hardware platform, the operating system and address the use of Off-The-Shelf software. This should be provided.

3. **Device (including software) Hazard Analysis: Possibly Acceptable**
The firm provided some risk analysis, but it is not clear that all the clinical hazards were identified. The firm should provide an enumerated description of the clinical hazards presented by this device, the causes and severity of the hazards, the method of control of the hazards and the testing done to verify the correct implementation of that method of control, and any residual hazards.

4. **Software Requirements Specifications (SRS): Possibly Acceptable**
The firm provided some Product Specifications. However, because the firm did not provide a Traceability Matrix, a complete review of this Section cannot be done. After an acceptable Traceability Matrix is provided, the review of the Section will be completed.

5. **Architecture Design Chart: Not Acceptable**
The firm did not provide a detailed depiction of functional units and software modules, which may include state diagrams as well as flow charts. This should be provided.

6. **Software Design Specification (SDS): Possibly Acceptable**
The firm provided some Product Specifications. However, because the firm did not provide a Traceability Matrix, a complete review of this Section cannot be done. After an acceptable Traceability Matrix is provided, the review of the Section will be completed.

7. **Traceability: Not Acceptable**
The firm did not provide a Traceability Matrix, which provides traceability among identified clinical hazards and mitigations, requirements, specifications, and verification and validation testing in an enumerated manor. This should be provided.

8. **Software Development Environment Description: Not Acceptable**
In several Sections the firm provided some description of the Software Development Environment. However, it seems incomplete. Thus, the firm did not provide a complete description of the software development environment, which should include a summary of the software life cycle development plan, an annotated list of the control documents generated during the development process, and the configuration management and maintenance plan documents. This should be provided.

9. **Verification and Validation Documentation: Possibly Acceptable**
The firm provided a description of some of the validation and verification activities. However, because the firm did not provide a Traceability Matrix, a complete review of this Section cannot be done. After an acceptable Traceability Matrix is provided, the review of the Section will be completed.

10. **Revision Level History: Not Acceptable**
The firm did not provide a revision history log, which provides the history of software revisions generated during the course of product development. This should be provided.

11. **Unresolved Anomalies (Bugs or Defects): Not Acceptable**
The firm did not provide a list of the remaining software anomalies, annotated with an explanation of the impact of the anomaly on safety or effectiveness, including operator usage and human factors. This should be provided.

12. **Cyber and Information Security: N/A**

13. **Run-Time Error Detection: Not Acceptable**
The firm did not include any information about what tools (such as a static analysis tool), if any, were used to detect software run-time errors. This should be provided.

RECOMMENDATION: ADDITIONAL INFORMATION REQUIRED

For the reasons specified supra, it is recommended that the firm should be asked for the following additional information before final approval is considered.

I will be happy to discuss these matters with the firm directly if that is more desirable. The following verbiage is offered as a possibility for inclusion in any oral or written correspondence with the firm.

If you have questions concerning these additional information requests, please contact Joseph Jorgens III on 301-796-2588.

Prior to submitting the additional information, please familiarize yourself with the following software guidance documents:

"Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices" (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089593.pdf) 5/11/05

"Guidance for Industry, FDA Reviewers and Compliance on Off-The-Shelf Software Use in Medical Devices" (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073779.pdf) (issued 9/9/1999)

"General Principles of Software Validation; Final Guidance for Industry and FDA Staff" (issued 1/11/2002) (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM085371.pdf)

You may also want to consider a review of the following consensus standards: IEC 62304:2006 (Medical device software – Software life-cycle processes) and ISO 14971:2000 (Medical devices - Application of risk management to medical devices).

For all the following information, please provide a table of contents with page numbers and tabbed sections, with each section repeating the question which is being addressed and clearly providing the answers to each of these additional information questions. If some of the information was provided in the original submission, please repeat that information in your response: do not just reference some previously submitted information.

1. **Level Of Concern**
You did not provide the Level of Concern.

The Agency considers these devices to have a MODERATE Level Of Concern. Please provide a MODERATE LOC statement.

2. **Software Description**
You did not provide a separate Section containing a Software Description.

Please provide a comprehensive overview of the device features that are controlled by software, and a description of the intended operational environment. This should include information on the programming language, the hardware platform, the operating system (if applicable) and the use of Off-The-Shelf software (if applicable).

3. **Device Software Hazard Analysis**
You provided some risk analysis, but it is not clear that all the clinical hazards were identified.

Please provide a description of the clinical hazards presented by this device and its products, the causes and severity of the hazards, the method of control of the hazards and the testing done to verify the correct implementation of that method of control, and any residual hazards.

Note: This is typically done in an enumerated columnar form, wherein the first column identifies the hazard to the patient, the second column identifies from where in the system that hazard could be caused, the third column presents, for software caused hazards, where in the software the hazard could be caused, and the fourth column provides the specific details of the mitigation including identifying the enumerated tests.

4. **Software Requirements Specifications (SRS)**
You provided some Product Specifications. However, because you did not provide a Traceability Matrix, a complete review of this Section cannot be done. After an acceptable Traceability Matrix is provided, the review of the Section will be completed.

After providing an acceptable Traceability Matrix, please review this Section. If edits are needed, please provide. If no edits are needed, please so state.

Please ensure that this Section provides your Software Requirements Specifications, which should clearly document the functional, performance, interface, design and development requirements in an enumerated fashion.

5. **Architecture Design Chart**
You did not provide an Architecture Design Chart.

Please provide a detailed depiction of functional units and software modules, which may include state diagrams as well as flow charts.

6. **Software Design Specification (SDS)**
You provided some Product Specifications. However, because you did not provide a Traceability Matrix, a complete review of this Section cannot be done. After an acceptable Traceability Matrix is provided, the review of the Section will be completed.

After providing an acceptable Traceability Matrix, please review this Section. If edits are needed, please provide. If no edits are needed, please so state.

Please ensure that this Section provides a Software Design Specification document, which describes how the requirements in the Software Requirements Specifications (SRS) are implemented. The information presented in the SDS should be sufficient to ensure that the work performed by the software engineers who created the software device was clear and unambiguous, with minimal ad hoc design decisions. The document that you submit should provide adequate information to allow for the review of the implementation plan for the software requirements in terms of intended use, functionality, safety and effectiveness. These should be presented in an enumerated manner, referencing the associated Software Requirements.

7. **Traceability**
You did not provide a Traceability Analysis.

Please provide a traceability matrix, which provides traceability among identified clinical hazards and mitigations, requirements, specifications, and verification and validation testing.

Note: This typically consists of a columnar matrix with line items for enumerated hazards, enumerated requirements, enumerated specifications, hazard mitigations and enumerated tests.

8. **Software Development Environment Description**
In several Sections you provided some description of the Software Development Environment. However, it seems incomplete.

Please provide a complete description of the software development environment, which should include a summary of the software life cycle development plan, and an annotated list of the control documents generated during the development process. Please include the configuration management and maintenance plan documents.

9. **Verification and Validation Documentation**
You provided a description of some of the validation and verification activities. However, because you did not provide a Traceability Matrix, a complete review of this Section cannot be done. After an acceptable Traceability Matrix is provided, the review of the Section will be completed.

After providing an acceptable Traceability Matrix, please review this Section. If edits are needed, please provide. If no edits are needed, please so state.

Please ensure that this Section provides a description of the validation and verification activities at the unit, integration, and system level. This should include the unit, integration and system level test protocols, including pass/fail criteria, test reports, summary and test results. Please include a description of any tests that were not passed, and any modifications made in response to failed tests and documentation demonstrating that said modifications were effective. Please include examples and a summary of the results. Please ensure that this is done in an enumerated manner.

10. **Revision Level History**
You did not provide a Revision Level History.

Please provide a revision history log, which provides the history of software revisions generated during the course of product development.

Note: This is typically a line-item tabulation of the major changes to the software during the development cycle,

including date, version number and a brief description of the changes in the version relative to the previous version. The last entry in the list should be the final version to be incorporated in the released device. This entry should also include any differences between the tested version of software and the released version, along with an assessment of the potential effect of the differences on the safety and effectiveness of the device.

11. Unresolved Anomalies (Bugs or Defects)

You did not provide a description of the unresolved anomalies.

Please provide a list of the remaining software anomalies, if any, annotated with an explanation of the impact of the anomaly on safety or effectiveness, including operator usage and human factors. If appropriate, please include any mitigations or possible work-arounds for the unresolved anomalies.

13. Run-Time Error Detection

What tools, (such as static analysis tools), if any, do you use to detect run-time errors. For any such tool used, please identify what error types the tool detects, your method and process of applying the tool(s), and a summary report and/or conclusion about the results.

Note: some common run-time errors are:

1. Un-initialized variables
2. Type mismatches
3. Memory leaks
4. Buffer over/under flow
5. Dead and unreachable code
6. Memory/heap corruption
7. Unexpected termination
8. Non-terminating loops
9. Dangerous Functions Cast
10. Illegal manipulation of pointers
11. Division by zero
12. Race conditions

Joseph Jorgens III -A

Digitally signed by Joseph Jorgens III -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300022581, cn=Joseph Jorgens III -A
Date: 2013.09.24 18:32:33 -04'00'

DATE: July 9, 2013

FROM: Barbara Cohen, Social Science Reviewer
through Lucie Yang, TL
through Shaw Chen, ODE IV Deputy Director,
Division of Nonprescription Clinical Evaluation Acting Division Director

SUBJECT: Technegen Generator System meeting package (NDA 202158, SD11)
Northstar Medical Radioisotopes LLC

TO: Division of Medical Imaging Products

Technegen Human Factors Social Science Review

Background

The TechneGen Generator System is a computer monitored and controlled automated synthesis module used to produce Sodium Pertechnetate Tc99m Injection without highly enriched uranium (HEU). The Tc99m is prepared using the Generator and then used to image a variety of different organs (via intravenous administration or direct instillation into bladder or eye) or to reconstitute a variety of reagent kits used for specific diagnostic imaging indications. Although there may be significant benefits to producing Tc99m without HEU, there are also many more steps for the nuclear pharmacist or technician involved when using TechneGen. Therefore, production of Tc99m using TechneGen results in a more significant potential for error.

Production of Tc99m using Ultra-TechneKow (NDA 017243) or TechneLite (NDA 017771) requires elution of only one column with sodium chloride. Once the eluate that contains Tc99m is checked for molybdenum breakthrough and alumina, the Tc99m can be administered to patients or used in a reagent kit.

In contrast, production of Tc99m using TechneGen generator requires the use of two columns. The lines are first washed with H_2O_2. The first column (ABEC, a separation cartridge) is prepared with [redacted] (b) (4) rinses. Once the alkaline potassium molybdate Mo99 is passed through the first column, there are multiple rinsing steps [redacted] (b) (4), sodium acetate x2) and an elution step (sodium chloride). The eluate from the first column is passed through a second column (alumina) which is eluted with sodium chloride and filtered prior to collecting the eluate in a vial. Although the ABEC column stays in the instrument for [redacted] (b) (4), whichever occurs

first, the alumina cartridge, sterilizing filter and filtration spike are disposable and must be replaced for each elution. Moreover, the system takes an hour when other systems only take a few minutes. The increase in the number of steps and solutions for washes / elutions (TechneGen compared to Ultra-TechneKow / TechneLite), as well as the time lapse involved with the potential for user distractions, significantly increases the potential for error. Not only is it necessary to check the eluate from the second column for molybdenum breakthrough and alumina, but it would also be important to check whether the pH of the Tc99m eluate is within acceptable range for human administration.

Previously in this NDA cycle, the company submitted an operator manual and a human factors study plan; these were discussed with the Sponsor and then revised by the Sponsor for this submission.

The Sponsor has resubmitted a human factors study plan for the TechneGen Generator System, which is still in development. DMIP has asked in a consult request to DNCE to review the protocol as below:

"*Please determine if the protocol is acceptable or not acceptable. If not acceptable please provide the changes needed to the protocol. Specifically: is the testing designed to be sufficiently sensitive to capture user errors; are critical tasks and use scenarios studied; are the instructions in the user manual adequately evaluated; are the methods for data collection acceptable and is sample size (e.g. numbers of users and user's trials) adequately justified?"*

This review will discuss the questions above (in a slightly different order for consistency of flow) and then provide sponsor-ready comments for DMIP's consideration (see page 8).

Protocol Assessment

1. **Are critical tasks and use scenarios studied?**

In the protocol provided, critical tasks have not been identified.

FDA Comments:
Identification of critical tasks would need to comprise a key component of a revised human factors protocol. Critical tasks should be noted as to whether they comprise efficacy issues, safety issues, or both.

Prior to finalizing the human factors protocols, the Sponsor should submit a document to FDA that discusses the critical hazards that could result from incorrect use of TechneGen. The Sponsor should identify the worst-case (catastrophic) scenarios for both the user and the patient, and the step of TechneGen use that an error could occur to result in the hazard scenario. The Sponsor should also create a table listing each potential hazard in a separate row (or column), and answer the following questions in separate columns (or rows).

- *How might they occur?*
- *How likely are they?*
- *What are the possible consequences of each?*
- *How might they be prevented?*

The Sponsor does state that performance evaluation scenarios shall be defined, including completion criteria. The Sponsor says that topics *may* (my italics) include:

- Source Mo99 connection
- Installation of Mo-Tc Reagent Kit components – inclusive of installing primary separation cartridge and waste vessel.
- Tc99m separation protocol, including Tc99m collection vial assembly and connection.
- Installation of Cleaning Kit components and execution of cleaning protocol.
- Initialization protocol
- Administrative tasks
- Recovery from error/fault conditions.

FDA Comments:
In a revised protocol, the Sponsor needs to document, in detail, all of the steps and scenarios that they are proposing, for the human factors study. FDA is not able to definitively evaluate a protocol that discusses scenarios that might be included.

2. Are the methods for data collection acceptable?

While the study will include both formative and analytical methodologies, the primary focus will be simulated use. Simulated use assessments will consist of training, training questionnaire, protocol performance, potassium molybdate Mo99 source connection and TechneGen usability performance questionnaires and debriefing interviews.

FDA Comments:
Simulated use is fine for an initial phase of study and it may be necessary for the entire study program given logistical considerations involving prototype(s). The Sponsor should consider direct observation in the natural work environment to assess how, based on the design and use, the Generator can safely and effectively be incorporated into the existing workflows of the personnel who will be using this product. If that is not possible, then a realistic environment with the associated workflows needs to be replicated as closely as possible in the simulated setting.

The defined user group includes qualified nuclear pharmacy or nuclear medicine department personnel. Page 39 of 113 of the meeting package defines Authorized User as "A nuclear pharmacist or technologist that has been trained by NorthStar or a certified NorthStar trainer."

FDA Comments:
The user groups in the human factors testing need to include a representative sample of anyone who would be using the product in real life (including, if applicable, users who have received no NorthStar training). Therefore the protocol needs more specificity as to which specialties will be assessed in human factors, as well as how many users of each specialty. Page 8 of the Human Factors Engineering/Usability Engineering report that was previously submitted by the Sponsor (General Correspondence submitted January 29, 2013) states: "While the training and experience of facility personnel expected to operate the TechneGen Generator System includes nuclear pharmacists, chemists, radiochemists, technologists and scientific disciplines with BS or advanced degrees, all operators must be qualified by training and experience in the processing and handling of radioactive materials and be experienced in aseptic processing techniques." Therefore, the Sponsor needs to clarify the inconsistency between the definition of authorized users in the meeting package and what was stated in the Human Factors engineering report.

No NorthStar employees or certified NorthStar trainers should be included in the sample used for the final human factors assessment.

Locations shall include a simulated nuclear pharmacy setting at Northstar, hospital or university-based nuclear medicine departments and/or licensed nuclear pharmacies. At least three separate locations will be identified and used from these three categories.

FDA Comments:
In addition to the three categories identified by the sponsor, generators are likely to be used in commercial centralized nuclear pharmacies such as Cardinal Health and nuclear medicine clinics. One outstanding question is whether they are envisioned to be used at all in mobile clinics. (All the above, with the exception of mobile clinics, were mentioned on p. 8. of the Human Factors Engineering/Usability Engineering report). Any type of sites in which it would be used should be adequately represented in the sample. If the generator is not to be used in mobile clinics, the Sponsor should explicitly state so.

Additionally, it's unclear what is meant by "at least three separate locations will be identified and used from these three categories." It's not clear whether this is referring to one location at each type of site, or three locations at each type of site. Other than at the NorthStar location, there should be more than one site for each type of clinic in the sample, given that different clinics may have different types of personnel, space configurations and work conditions.

The number of participants for the simulated use portion of the study is estimated at greater than or equal to 15, with each participant performing 1-3 sessions plus training.

FDA Comments:
It's not clear what the Sponsor means by 1-3 sessions; for instance, this could involve duplicative sessions for each study participant assessing the same tasks after training and

retraining. Conversely, it could involve assessments of different tasks in each session. The Sponsor needs to provide much more specificity on this. Final testing should involve only one session per set of tasks per participant.

TechneGen systems used in conducting this study shall be controlled and their configurations documented. The locations used for the study shall meet TGS installation requirements and installations shall be qualified and documented.

FDA Comments:
This is fine for initial testing. However, see above comment regarding direct observation in the natural work environment. In any case, the Sponsor will need to perform some testing under simulated conditions of time pressure, continued interruptions and poor lighting.

According to the NDA Orientation Sponsor's version meeting minutes of February 5, 2013 (pp 3-4), although NorthStar supplies the computer and controls the software, it's possible to actually lose host computer communication with the TechneGen instrument and the instrument will operate independently. If a protocol is running, once communication is re-established the host computer will resynchronize with the instrument providing a graphical display of protocol status, so that the material being prepared is not lost.

Therefore, loss of the computer connection should be one of the scenarios tested.

Usability metrics will be gathered and reported by the facilitator (a NorthStar employee or contractor). Sessions may be videotaped but the video may not be posted, published or used beyond NorthStar authorized employees.

FDA Comments:
The facilitator cannot be a NorthStar employee or a trainer; it must be an independent contractor. Videotaped sessions should be able to be made available both to the human factors consultant and to FDA upon request.

If assistance is given by the facilitator or others, the facilitator will record the details of the interaction and the session will be reported as dependent completion.

FDA Comments:
In the final study, no assistance to users should be provided of any kind, as that will likely be the situation most encountered in real life. The Human Factors Engineering/Usability Report discusses, on page 6, that "all authorized sites are required to have a radiation safety officer, or equivalent as required by respective state licensing to oversee the safe use, handling and processing of radioactive materials." The Sponsor should clarify the

envisioned role and training of these individuals at each site with respect to the Generator.

Additionally, the sessions should be one-on-one, with no other subjects present to provide assistance or model the correct approach.

Metrics include completion, success, independence, adherence to application dialogs and error rates. In addition, TGS fault rates and subjective evaluations will be gathered. Time to completion of sessions and defined session midpoints will also be gathered.

FDA Comments:
Metrics should include objective quantifiable factors as well as subjective ones. For instance, metrics should include whether the pH of the final eluate is within acceptable range for human administration, whether the level of molybdenum breakthrough is within acceptable range, and the whether the specific activity is within acceptable range. The acceptable ranges should be pre-specified and justified in the protocol.

It also appears that your protocol does not assess the percent of users who complete every step correctly (this includes having an acceptable bioburden after use). Please add this as a metric.

3. Are the instructions in the user manual adequately evaluated?

The Sponsor has submitted revised user manuals. In the proposed human factors testing, all sessions will be open book – all training materials and user manuals shall be available to participants.

FDA Comments
Because the human factors testing is essentially an "open book test" where users can look both at the training materials and the user manuals, there does not appear to be an evaluation included of the user manual on a standalone basis. However, since training materials can disappear over time, it's critical to determine whether the user manual can stand on its own. Therefore, there should be a segment of trained users tested with only the user manual.

Additionally, according to the Sponsor's version of the minutes of the February 2013 NDA Orientation meeting, FDA stated (p.5) that the user manual will be considered to be part of the labeling section of the NDA. Therefore, the Sponsor should conduct a type of label comprehension study to test the user manual first with a representative sample of potential users in order to optimize comprehension prior to using the manual in a human factors assessment. Note that as a result of the human factors assessment, the label may need to be revised again.

4. **Is the sample size (e.g. numbers of users and user's trials) adequately justified?**

FDA Comments:
This cannot be evaluated in the current protocol. In a revised protocol, the Sponsor should propose a sample size incorporating all of the factors in the above discussion, and provide a detailed justification. FDA will then be able to assess whether this is adequate.

5. **Is the testing designed to be sufficiently sensitive to capture user errors?**

FDA Comments
It's impossible to address this question with the current protocol. When a revised protocol is provided with the critical steps to be assessed, the exact scenarios that will be tested and a representative sample size with justification, the sensitivity of the test can be evaluated.

Additional Comments for DMIP:

1) *The above comments represent preliminary feedback from FDA and additional detailed feedback would be provided upon further development of the human factors testing program in conjunction with a highly experienced testing firm in the field. All final protocols should be submitted to FDA for review and comment prior to implementation of testing. FDA may consult with outside experts in its final protocol review.*

2) *We note that the Generator is still in development, and the Sponsor makes references to at least two iterations of human factor testing. The initial phase will be conducted using the prototype TechneGen generators that were used to perform the process validation studies that were included in the NDA, while the final phase will include Human Factors evaluation of an improved second generation TGS, which will incorporate user design enhancements but will employ the identical separation and purification processes. While it is a good idea to incorporate iterations in the development of the final product to be tested, the final human factors test needs to be a standalone assessment, and cannot incorporate any people who participated in previous tests.*

3) *At the time that the critical hazards are submitted to FDA, we also request that the Sponsor submit an accompanying document that details any significant differences in Technegen components from currently marketed products, which could have an impact on users. For instance, hypothetically if a column was smaller than one in the current products, it could be more difficult for a user with visual or dexterity problems to correctly use the product. In that instance, we*

would probably then request that such users be incorporated into the final human factors testing.

SPONSOR-READY COMMENTS FOR DMIP's CONSIDERATION (in response to Sponsor question 2 in the meeting package regarding the human factors protocol):

A. Preparation for Human Factors Study

i. We strongly recommend that you engage a highly experienced human factors testing firm with specific expertise in engineering of medical products similar to TechneGen.

ii. Prior to finalizing the human factors protocols, please submit a document that discusses the critical hazards that could result from incorrect use of TechneGen. Identify the worst case (including catastrophic failure) scenarios for both the user and the patient, and the corresponding step of TechneGen use that an error could occur in to result in the hazard scenario. You should also create a table listing each potential hazard in a separate row (or column) and answer the following questions in separate columns (or rows)

- **How might they occur?**
- **How likely are they?**
- **What are the possible consequences of each?**
- **How might they be prevented?**

iii. Along with the critical hazards document, please submit an accompanying document that details any significant differences in TechneGen components – that would be handled by the user – that differ from currently marketed products. For instance – are the TechneGen columns larger, smaller, or the same size as other products? If the columns are not directly handled by the user, please also comment on components that would be directly handled by the user. We are asking for this information to assess whether users representing varying levels of visual acuity and dexterity should be incorporated into the protocol.

B. Critical Tasks / User Steps

i. When you submit a revised human factors protocol, please identify critical tasks for the user to accomplish correctly and indicate whether failure to accomplish each individual task would constitute a safety issue, an efficacy issue, or both.

ii. Please document in detail all of the user steps and scenarios that you are proposing for the human factors study.

C. User Manual

i. As the user manual is considered part of the labeling section of the NDA, you will need to conduct a label comprehension study to test the user manual first with a representative sample of potential users in order to optimize comprehension prior to using the manual in a human factors test. Note that as a result of the human factors assessment, the label may need to be revised again.

ii. The user manual needs to be evaluated on a stand-alone basis, and not just in conjunction with the training materials. Therefore, in your human factors study, there should be a segment of trained users tested with only the user manual.

D. TechneGen Users / Study Subjects

i. Page 39 of 113 in the meeting package defines Authorized User as "a nuclear pharmacist or technologist that has been trained by NorthStar or a certified NorthStar trainer." However, page 8 of 64 of the Human Factors Engineering/Usability Engineering Report (submitted January 29, 2013) states that "while the training and experience of facility personnel expected to operate the TechneGen Generator System includes nuclear pharmacists, chemists, radiochemists, technologists and scientific disciplines with BS or advanced degrees, all operators must be qualified by training and experience in the processing and handling of radioactive materials and be experienced in aseptic processing techniques." Please clarify the anticipated users of this product, given the apparent inconsistencies between these two documents, and include sufficient representation of all types of users in the revised protocol.

ii. While it is a good idea to incorporate iterative testing into the development of the final product, the final human factors test needs to be a standalone assessment and cannot incorporate any subjects who participated in previous tests.

E. Radiation Safety Officer

The Human Factors Engineering/Usability Report discusses, on page 6 of 84, that "all authorized sites are required to have a radiation safety officer, or equivalent as required by respective state licensing to oversee the safe use, handling and processing of radioactive materials." Please clarify the envisioned role and training of these individuals at each site with respect to the Generator.

F. Testing Facilitators

Testing facilitators should not be NorthStar employees or trainers; these should be independent contractors.

G. Testing Sites / Conditions

i. Consider direct observation in the natural work environment (if logistically feasible with prototype(s)) as well as simulated use. In any case, you most likely will need to perform some testing under conditions of time pressure, continued interruptions and/or poor lighting.

ii. In the meeting package, page 16 of 113 states that "locations shall include a simulated nuclear pharmacy setting at NorthStar, hospital or university-based medical departments and/or licensed nuclear pharmacies. Page 7 of 64 of the Human Factors/Usability Engineering report states, "The types of facilities that the TechneGen Generator System will be operated in are identified in the following list: Commercial nuclear pharmacies; nuclear pharmacies (academic centers); hospital based nuclear medicine departments; nuclear medicine clinics." Authorized users from all types of sites where the product may be used should be included in the protocol. Therefore, please include users from commercial nuclear pharmacies, nuclear medicine clinics and mobile clinics, if applicable. If direct observation in the natural environment is not used, the environment should simulate as much as possible the differing work conditions represented by the various sites.

iii. Please specify what is meant by "at least three separate locations will be identified and used from these three categories" (section 5.1.2, page 16 of 113). It is unclear whether this is referring to one location at each type of site or three locations at each type of site.

iv. In the final study, no assistance of any kind should be provided to users, since that will likely be the situation most encountered in real life.

H. Sessions

i. Please specify what is meant by "each participant performing 1-3 sessions" (section 5.1.1, page 16 of 113). Do these involve duplicative sessions assessing the same tasks, or an assessment of different tasks in each session? Final testing should include only one session per set of tasks per participant.

ii. Additionally, the sessions in the study should be one on one, with no other subjects present to provide assistance or to model the correct approach.

I. Videos

Page 18 of 113 of the meeting package states that videos will not be posted, published or used beyond NorthStar authorized employees. Please clarify your definition of "NorthStar authorized employees" and confirm that videos can be made available to the human factors testing company and to FDA upon request.

J. Metrics

Metrics should include objective, quantifiable factors as well as subjective ones. For instance, metrics should include whether the pH of the final eluate is within acceptable range for human administration, whether the level of molybdenum breakthrough is within acceptable range and whether the specific activity is within acceptable range. The acceptable ranges should be pre-specified and justified in the protocol. It also appears that your protocol does not assess the percent of users who complete every step correctly (this includes having an acceptable bioburden after use). Please add this as a metric.

K. Sample Size

Please provide a revised estimate of sample size for the human factors study, incorporating all of the discussion above.

L. The above comments represent preliminary feedback and additional feedback may be provided upon receipt of the revised protocols and other materials as requested above. We recommend that you submit final protocols to FDA for review and comment prior to implementation of testing.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BARBARA R COHEN
07/15/2013

LUCIE L YANG
07/15/2013