CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202158Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	January 26, 2018
From	Eldon E. Leutzinger, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA	202158
Applicant	Northstar Medical Radioisotopes, LLC
Date of Submission	May 8, 2017 (Resubmission)
PDUFA Goal Date	February 8, 2018
Proprietary Name / Established (USAN) names	RadioGenix™ System (Technetium Tc 99m Generator) for production of technetium Tc 99m injection, USP
Dosage forms / Strength	Sterile solution;
Proposed Indication(s)	For intravenous, intravesicular and ophthalmic use; reconstitution of technetium radiopharmaceutical kits
Recommendation:	Approval

1. Introduction

NDA 202158 was submitted by Northstar Radioisotopes, LLC on January 4, 2013 as a 505(b)(2) application, and received on the same date. After completion of its review, it was determined that the NDA could not be approved, due to multiple deficiencies from clinical, product quality microbiology, product quality CMC, labeling, and deficiencies regarding manufacturing facilities. There was determined a need for a safety update to include data from all nonclinical and clinical studies/trials of the drug regardless of indication, dosage form and dose level. As well, there were also concerns from CDRH.

On May 8, 2017 Northstar Radioisotopes resubmitted the NDA (acknowledged, June 2, 2017) as a response (class 2) to address the deficiencies in the Complete Response Letter of November 4, 2013. A major amendment was received on October 13, 2017 which extended the goal date by three months (February 8, 2018) to provide time for a full review of the submission.

The disciplines and reviewers who assessed this NDA are listed in Table 1.

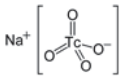
Table 1. FDA Disciplines and Reviewers Involved in the Evaluation of NDA 202158

Discipline	Reviewer	Team Leader
Chemistry, Manufacturing and Controls		
Drug Product	Dr. Ravi Kasliwal	Dr. Danae Christodoulou
Drug Substance	Dr. Ravi Kasliwal	Dr. Danae Christodoulou
Facility	Dr. Krishnakalli Ghosh	Dr. Juandria Williams
Microbiology	Dr. Jessica Chiaruttini	Dr. John Metcalfe

Non-Clinical	N/A	N/A
Clinical Pharmacology/Biopharmaceutics	NA	N/A
Clinical	Dr. Phillip Davis, MD	Dr. Libero Marzella
CDRH	Robert Meyer, M.S.	John McMichael, Ph.D.
Labeling Division of Medication Error Prevention and Analysis (DMEPA) DPMH ADL - DMIP	Idalia Rychlik Erica D. Radden, MD N/A	Danielle M. Harris/Quynhnhu T. Nguyen, MD (Assoc. Dir) Mona K. Khurana, MD Dr. Michele Fedowitz, MD

2. Background

The **RadioGenix System** is a new version of the technetium generator (^{99}Mo / ^{99m}Tc), intended to be used in a nuclear pharmacy to produce Sodium Pertechnetate Tc 99m Injection USP,



, where Tc = ^{99m}Tc ($t_{1/2}$ 6 hrs, and γ radiation of 140.5 KeV). The System is designed to be used with ^{99}Mo derived from non-fission processes, e.g., ^{98}Mo(n,γ)^{99}Mo, and of low specific activity. $^{99m}TcO_4^-$ is generated on decay of ^{99}Mo (half-life of 66 hrs) in the oxyanion of molybdate,

, the structure of which is approximately preserved in pertechnetate [$^{99}Mo(VI)O_4^{2-} \rightarrow {}^{99m}Tc(VII)O_4^- + \beta^- + \acute{\upsilon}$(antineutrino)]. The tetrahedral structure for molybdate ($^{Nat}MoO_4^{2-}$) is well-accepted, having its origin of structure proof dating back to the mid 1960's [*R. H. Busey and O.L. Keller, Jr., Journal of Chemical Physics 41, 215 (1964)*, through Raman crystal spectra. These investigators also showed by correlation of Raman aqueous spectra of molybdate and pertechnetate ($^{99}TcO_4^-$) that the structure of the latter oxyanion was also tetrahedral.

The change from ^{99}Mo to ^{99m}Tc, all within the oxyanion molecular framework, does not just passively happen. **At the point of transmutation, there is a "recoil" by the daughter nucleus (^{99m}Tc). The recoil energy depends on the energy of the β^- and ν' (antineutrino) particles, and their emission directions. It is known that recoil energies exceed most bond energies**. Since the ^{99m}Tc nucleus remains attached in the oxyanion, this recoil energy is redistributed in the molecular framework of the oxyanion (i.e., among the Tc-O bonds). Thus, it is interesting that damage is not done to the oxyanion, such that it changes the molecular structure (e.g., to a different oxyanion) during recoil, given the heavy Tc nucleus. However, retention of the oxyanion structure in the product (as was initially present in the

parent system) is apparently maintained, including the tetrahedral geometry. That this is so for the $^{99}Mo/^{99m}Tc$ system is fortunate, for if it were not, that would likely change the entire landscape of the radiochemistry of the technetium generator ($^{99}MoO_4^{2-} \rightarrow {}^{99m}TcO_4^- + \beta^- + \nu$'), and all of the subsequent chemistries during radiolabeling of the technetium radiopharmaceuticals kits. Further discussion of this curiosity is beyond the scope of this document, but is mentioned here, because it is a testimony to the robustness of the technetium generator, seemingly appropriate with the timing of the RadioGenix System, as it represents the first major advance in the long saga of the technetium generator.

In its earliest form, the technetium generator was invented at the Brookhaven National Laboratories in 1957. It became available in 1960 from BNL, but did not become commercially available until 1964. It was first approved as UltraTechnekow (Curium/Covidian/Mallinckrodt) by the FDA in 1973. A second approval occurred in 1976 (as Technelite by Lantheus), and again in 2013 (as Technetium Tc 99m Sodium Pertechnetate Generator by GE Healthcare).

Working Principle of the RadioGenix System

Use of low specific activity ^{99}Mo with the RadioGenix System is made possible by use of an ABEC column (Aqueous Biphasic Extraction Chromatography), connected in series with an Alumina column (aluminum oxide). Together with ancillary equipment consisting of tubing lines and valves, the System is housed in a computer-controlled synthesis module. The ABEX column is filled with monoethylated polyethylene glycol (PEG), chemically bonded to styrene-divinylbenzene resin beads. $^{99}MoO_4^{2-}$ in 5M KOH (alkaline pH) is loaded onto the ABEC column. (b) (4) so that $^{99m}TcO_4^-$ is retained on the ABEC column, while $^{99}MoO_4^{2-}$ passes through and is recovered. The ABEC column is subsequently rinsed with 5M KOH, whereupon the removal of all $^{99}MoO_4^{2-}$ is completed. Following loading and washing (5M KOH, followed by 1.5M sodium acetate), $^{99m}TcO_4^-$ is removed from the ABEC column with saline. This saline eluate is routed to an Alumina column. Any $^{99}MoO_4^{2-}$ left in the eluate from ABEC is retained on Alumina. Elution of the Alumina column (in reverse-flow) with saline affords the Sodium Pertechnetate Tc 99m Injection USP ($Na^{99m}TcO_4$). Reverse-flow cuts down on the amount of fluid volume that must be used to remove the $^{99m}TcO_4^-$ from its band at the top of the ABEC column.

Addition of ABEC separation technology is the distinguishing feature that makes RadioGenix System unique in the panel of approved technetium generators, the novelty of which creates a potential solution to the problem of the absence of a U.S. source of ^{99}Mo, a problem exacerbated by the impending switch from HEU to LEU in the production of ^{99}Mo.

How ABEC Works -

Although the mechanism of metal ion partitioning in ABEC is poorly understood, it is a proven technology, having its roots in a type of LC, based on aqueous biphasic principles for which there is a significant body of experimental work. According to current theory, there is a thermodynamic basis for metal ion partitioning in ABS (aqueous biphasic systems). At high ionic strength, ions (such as TcO_4^-), having a relatively small negative Gibb's free

energy of hydration (ΔG_{hyd}), tend to partition to the PEG-rich phase in ABS – "salt out," whereas those (such as for MoO_4^{2-}) that have large negative free energy of hydration move into the aqueous-phase. Since both biphasic systems are PEG-based, similar behavior occurs with ABEC, so that TcO_4^- is retained in the polystyrene-bonded PEG, while MoO_4^{2-} is excluded, the latter passing into the aqueous phase. At low ionic strength, the distribution changes, and TcO_4^- is no longer retained in the polystyrene-bonded PEG phase in ABEC [*G. Huddleston, et.al., in Metals in Biotechnology, Vol.11, Humana Press, Inc., Tolowa, N.J*].

3. Product Quality

From a CMC standpoint, product quality is both describable and controllable through certain attributes considered as critical, i.e., **Critical Quality Attributes**. For the RadioGenix System, these CQA's relate to the quality of the Sodium Pertechnetate Tc 99m Injection and to the capability of the System to produce it reproducibly, and sterile, in the hands of a standard nuclear pharmacy. In summary, **there were multiple deficiencies impacting these CQA's**, ranging from the absence of optimized flow rates and their maintenance in the commercial generator, to the absence of critical quality attributes of ABEC (including leachables and stability), absence of information on associated kits (Reagent Kit, Cleaning Kit, Collection Kit), and performance testing of the generator eluate in Ceretec (and implication to other technetium radiopharmaceutical kits), to generator manufacturing. Numerous deficiencies were found in the labeling. Each of these CQA's, the attendant deficiencies, and their resolution are briefly described as follows:

Optimized flow rates -

Visualized as a sort of CQA, the rate of flow of fluid through the ABEC column relates to the capability of ABEC to perform its function in the generator. **The ABEC column is the pivotal component in the RadioGenix System, since it's critical function is to extract $^{99m}TcO_4^-$ from the $^{99}MoO_4^{2-}$ source and concentrates it on the column**. Chromatography theory of separation by partition processes dictates that there is an equilibrium involving mass transfer of solutes between mobile and stationary phases. **Too fast a flow rate may override this equilibrium, shifting its position enough toward the mobile phase to alter the distribution ratio to adversely affect the capability of the ABEC mechanism to establish efficient selectivity between $^{99}MoO_4^{2-}$ and $^{99m}TcO_4^-$, putting the latter at risk of not being fully extracted from the source**. There are two other accompanying critical corollaries. One (1) is that the $^{99m}TcO_4^-$ needs to remain sequestered on ABEC during the rinsing step ((b) (4) 1.5M sodium acetate) to enable efficient extraction. Secondly (2), the $^{99m}TcO_4^-$ needs to come off ABEC in as small volume of saline as possible so that it can be fed onto the Alumina column to assure final strengths (mCi/mL) of $^{99m}TcO_4^-$ similar to those from the conventional technetium generator. With the information provided in the resubmission, the flow rates have been optimized, and the issue resolved.

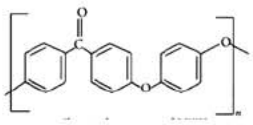
ABEC Media (for ABEC column) -

The foregoing on flow rates is a play on performance of the ABEC column in terms of the importance of flow rates in determining the distribution of $^{99m}TcO_4^-$ and $^{99}MoO_4^{2-}$ between stationary and mobile phases. Although not a CQA, per se, the chemical and physical characteristics of ABEC media influences its capability to perform its critical function, and in the end influences the quality of the Sodium Pertechnetate Tc 99m Injection USP that is the

product produced by RadioGenix System. These chemical and physical characteristics take on the same weight in the same sense as CQA's. The chemical characteristics influence the stability of the ABEC media. The physical characteristics (b) (4) That is important to obtain a strength of the final product (Sodium Pertechnetate Tc 99m Injection USP) comparable with that in the approved technetium generators.

Leachables -

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



It has a history of great stability against chemical and radiological insult, the latter based on the resistance of its molecular framework to attack by free radicals. In like manner, the robustness of its structure imparts documented stability towards attack by ozone, making PEEK compatible with the procedures for sterilization of the internal portions of the generator system. Nevertheless, NorthStar initiated a study for leachables, in accordance to USP <87> and USP <660>, subjecting to ozonated water, KOH, (b) (4) γ radiation. (b) (4) was performed at Argonne National Labs with a Van De Graaff Generator. Gamma radiation was performed at (b) (4) Ozonated water and KOH studies were performed at NorthStar Madison, WI. The results of these studies demonstrated that the PEEK and other materials within the internal system was resistant to the reagents and radiation (consistent with the history of the properties of PEEK).

Reagents –

Product quality and stability of reagent solutions are important for maintenance of the capability to carry out their functional roles in the operation of radionuclide generators. The most critical of these issues for reagents comprised the *alkaline reagent solution (ABEC rinsing)* in plastic containers, since it is used in the loading of the $^{99}MoO_4^{2-}$ onto ABEC, and its subsequent rinsing to remove all traces of $^{99}MoO_4^{2-}$. In addition to the criticality of the ABEC rinsing solution (alkaline), there are the associated *"Kits" in support of the operation of the generator,* ***Reagent Kits*** *(in-process reagent solutions of 3% H_2O_2, 5M KOH, 1.5M Sodium Acetate),* ***Primary Separation Cartridge wit ABEC resin****, the* ***Tc99m Product Kit***, and a ***Sterilization Kit***. A change was made in the alkaline reagent, from (b) (4) to KOH, better suited to achieving stability over a proposed (b) (4) year expiration dating period. To better define

these kits and their better controls, NorthStar developed new versions, including Reagent Kit, Sterilization Kit and Tc99m Product Kit and described in the RadioGenix Operator Guide.

NorthStar added [redacted] (b) (4) as a new supplier for the reagent bags, creating additional CMC and microbiology issues (as well as those regards the CGMP status of the manufacturing facilities. The amendment was made a major amendment, and a letter was issued to Northstar that the user fee goal date was extended to February 8, 2018.

Performance Testing -
As radionuclide generators age (toward expiry), radioactivity of the eluates become less, and with that come the necessity for use of larger volumes to get enough radioactivity to offset its decline with time. This became evident in the radiolabeling Ceretec with Radiogenix pertechnetate, where many failures were observed (with stabilized and unstabilized kits). This was also noted (in terms of failed radiochemical purity) for Sestamibi and MAG2 kits. Subsequent studies led to the implementation of a volume threshold for each type of kit (anionic, cationic, and neutral). A volume limit of 1 mL of RadioGenix Sodium Pertechnetate Tc99m Injection is recommended for reconstituting Ceretec kits, 3.0 mL for Sestamibi kits and MAG3 kits, thus resolving this issue.

The use of H_2O_2 in the routine sterilization of the internal parts of the RadioGenix System presents a situation not encountered before (reference to the approved technetium generators). The result of this sterilization procedure, H_2O_2 residues result in the Sodium Pertechnetate Tc 99m Injection (issue raised in the review by Ravi Kasliwal). **This point is important, although it is not clear at this point what its ultimate significance will be, something that will need to be assessed as experience with the generator proceeds**. The importance is signaled by the fact that most of the technetium radiopharmaceutical kits carry a warning to the user not use Sodium Pertechnetate Tc 99m Injection that contains any oxidants (or additives, the latter with implication of presence of oxidants), since such substances will oxidize the stannous chloride ($SnCl_2$) to stannic chloride $SnCl_4$), thus depleting the kit of Sn^{2+}, necessary for reduction of $^{99m}Tc^{7+}$to an oxidation state suitable to radiolabel the ligand in the kit. **Since larger volumes of pertechnetate will contain larger amounts of peroxide, care needs to be given to use as little volume of Sodium Pertechnetate Tc 99m Injection as possible to prevent this interference with radiolabeling Tc99m radiopharmaceutical kits. It is recommended that these directions be incorporated into the labeling**.

As a follow-up, a **PMC for Product Quality** is put in place, comprised of two components. In the first (1) of these, NorthStar will perform studies to evaluate the effectiveness of radiolabeling all commercially available technetium Tc 99m drug product kits in the US (except for Ceretec, Sestamibi and MAG3), as per kit manufacturer's directions using representative sodium pertechnetate Tc 99m injection solutions obtained from 3 different RadioGenix Systems. The studies for each kit will cover different volumes (from low to high end range) of sodium pertechnetate Tc 99m injection solutions obtained throughout the 14-day shelf-life of the potassium molybdate Mo 99 source. The PMC Milestones are as follows:

Final Protocol Submission: 04/15/2018
Study/Trial Completion: 04/15/2019

Final Report Submission: 06/15/2019
Interim Report: 11/15/2018

(b) (4)

4. Microbiology Product Quality

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

PMR-

Details of the PMR, and dates for completion are as follows (reproduced from the Facsmile from the FDA, dated 01/05/2018. See the next page. In the original facsimile (01/05/2018), it is indicated as a PMR.

PMR #1 description:
Evaluate the fluid path bioburden and final product endotoxins and sterility in the RadioGenix system at interim timepoints and the instrument expiry from diverse clinical sites.

PMR Schedule Milestones:

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

PMR #2 description:
NorthStar will perform studies to evaluate effectiveness of radiolabeling all commercially available technetium Tc 99m drug product kits in the US (except the ones already evaluated in NDA 202158), as per kit manufacturer's directions using representative sodium pertechnetate Tc 99m injection solutions obtained from three different RadioGenix Systems. The studies for each kit will cover different volumes (from low to high end range) of sodium pertechnetate Tc 99m injection solutions obtained throughout the 14-day shelf life of the potassium molybdate Mo 99 source. The effectiveness study must verify that the radiolabeled kits meet the quality requirement listed in the kit manufacturer's package insert. NorthStar agrees to amend the RadioGenix System labeling based on the result of the study, as appropriate.

PMR schedule milestones:

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

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

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

5. CDRH

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

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

A letter was received from NorthStar (January 22, 2018), proposing the following schedule milestones for satisfying this PMC (schedule milestones deemed satisfactory by CDRH):

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

6. Human Factors Study

In summary, the HF validation study and supporting documentation was found to be acceptable (review by Idalia E. Rychlik, DMEPA, 01/12/2018). Together with nuclear pharmacy standards, their analysis of the Operator's Guide, instructional videos and training outlined by NorthStar, as well as examination of root cause of errors, participants responses, its is concluded **there is a reasonable level of expectation that licensed nuclear pharmacies should be able to use the RadioGenix System in a safe and effective manner**. In the HF study, 30 participants (15 nuclear pharmacies, and 15 nuclear pharmacy technicians) committed 48 critical errors and 16 close calls while performing the tasks using the RadioGenix System. However, NorthStar determined that the current risk controls were effective in mitigating these errors. All of the tasks and errors committed were analyzed in the HF study. On receipt of a RadioGenix System by a licensed nuclear pharmacy, all nuclear pharmacists and technicians using the System will complete a training program administered through NorthStar. This program will be representative of real use, and will be conducted over a 6 – 8 hour period. That will consist of 3 components: (1) lecture/presentation on the system operation and videos, (2) hands on training with simulated RadioGenix System, and (3) addition of hands on practice time for users. Users will have continuous access to the RadioGenix Operator's Guide and step-by-step video tutorials.

What might be notable is the observation in the HF study that some participants appeared to be confused about the difference between the "red stop button" and the "stop protocol button" on the interface. This is tagged as a point that should be better emphasized in the training. Despite this, it is indicated in the HF study that none of the participants used these buttons incorrectly. Together with these overall observations, the conclusion in the HF study is that all the current risk control measures are effective in mitigating use errors.

7. Facilities

In accordance to the manufacturing facilities review (Krishnakalli Ghosh, Ph.D., 01/16/2018), there are no outstanding manufacturing or facility risks that prevent approval of NDA 202158. There had been major concerns regarding two sites (Madison, WI, and Columbia, MO) for the RadioGenix System and system components, and with (b) (4) (a contract testing site) following PAI inspections. The observed deficiencies were addressed with corrections made. A final re-inspection was made at (b) (4), due to the nature of the deficiencies (resulting in a withhold letter). Final responses to the FDA 483 was reviewed for the 5 PAI inspections, and found to be adequate for all the inspected sites.

8. Labeling

There have been considerable need for changes in the labeling, that also includes the immediate container for Sodium Pertechnetate Tc 99m Injection USP, vial shield label and the label for the generator itself. The specifics regarding the CMC information in each of these labels is spelled out in the final review of the Drug Product (Ravi Kasliwal, Ph.D.). DMEPA also had comments on the carton and container labels. Requests for this information (including that from CMC, DMEPA and Michele Fedowitz, MD of DMIP) was conveyed to the sponsor on January 12, 2018; this included recommendations for label of the final Product

Vial (Collection Vial), the Shield Label, as well as specific comments from DMEPA. It is recommended that the drug label be as follows, based on the history of labeling of the currently approved technetium generators:

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

The Division of Pediatric and Maternal Health (DPMH) had identified concerns regarding the population and indications for which the product is approved (as well as the basis for that approval), review by DPMH (Erica D. Radden, MD., 01/17/2018). Language was added to the label (package insert) to indicate that use has been established in the entire pediatric population (ages 0 – 17) for thyroid and vesico-urethral imaging. It is pointed out in the pediatrics review that the ultimate determination of dosing (Dosing and Administration section) should use the smallest dose possible and yet be able to obtain acceptable quality diagnostic information. Also, included was that this section should note safety concerns specific to the pediatric population (as the risks are greater in pediatric than for adults), and the labeling should clarify the adult indications for which the product is not approved in pediatric patients. Hence, the advice from DPMH is that there should be language indicating that the safety and effectiveness has not been established in pediatric patients for salivary gland and nasolacrimal drainage system imaging.

9. Risk Benefit Assessment

Recommended Regulatory Action
Approval.

Risk Benefit Assessment
The RadioGenix System is a version of the technetium generator. The approved technetium generators have an established history of safe and effective use, dating to 1973. RadioGenix System is a more complex system that provides the same product (Sodium Pertechnetate Tc 99m Injection USP), but requires more attention of the user than in the conventional version. However, as the human factors study has demonstrated, with proper training, the RadioGenix System can be used in nuclear pharmacies under standard nuclear pharmacy practice. The theory, manufacture and use of this generator has undergone intense scrutiny from the Product Quality, Microbiology Product Quality, CDRH, manufacturing facilities, as well as clinical / labeling and human factor components. Considering the risks, the consensus from all these review disciplines is that the risk is at a reasonable level to assure safe and effective use of the RadioGenix System. Nevertheless, because of the complex nature of the RadioGenix System, NorthStar has been directed (by FDA) to put into place a protocol for "Annual Preventive Maintenance" that will list all items to be replaced, along with details of what will be done as part of the maintenance procedures and how the operational qualification (OQ) of the system will be performed.

In summary, I am referencing the September 26, 2013 NDA review titled: Deferral of Risk Evaluation and Mitigation Strategies." At that time the Office of Medication Error and Risk Management concluded that multiple NDA deficiencies (involving system design and performance, microbiological quality control, human factors study, and operator manuals)

precluded an assessment of the need for a risk evaluation and mitigation strategy (REMS). All these deficiencies have been addressed in this NDA resubmission. NorthStar did not submit a REMS, and because there are no outstanding issues a REMS is not needed.

There are multiple benefits offered by the RadioGenix System. One is to resolve the issue of absence of a domestic source of ^{99}Mo, which has been exacerbated by aging nuclear reactors outside of the US, causing intermittent downtime, shortages, and thus adversely affecting Public Health. Secondly, the RadioGenix System comes at an opportune time to potentially help meet the looming mandate in the interest of National Security to convert from HEU to LEU in the production of ^{99}Mo.

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

/s/

ELDON E LEUTZINGER
01/26/2018

Cross-Discipline Team Leader Review

Date	**October 11, 2013**
From	**Eldon E. Leutzinger, Ph.D.**
Subject	**Cross-Discipline Team Review**
NDA	**202-158**
Applicant	**Northstar Medical Isotopes, LLC**
Date of Submission	**January 01, 2013**
PDUFA Goal Date	**November 04, 2013**
Proprietary Name	**TechneGen Generator System**
Established Name	**Sodium Pertechnetate Tc99m Injection USP**
Dosage Forms /Strength	**Sterile solution; strength variable**
Proposed Indications	**Brain, salivary gland, blood pool, urinary bladder, nasolacrimal draining system imaging; reconstitution of technetium radiopharmaceutical kits**
Recommended	**(CR) Complete Response**

1. Introduction

The TechneGen Generator System is a version of the technetium generator (^{99}Mo / ^{99m}Tc), but which allows for use of low specific activity ^{99}Mo. TechneGen is intended for use in a nuclear pharmacy and produces Sodium Pertechnetate Tc 99m Injection USP. The applicant is NorthStar Medical Isotopes, LLC (5249 Femrite Road, Madison, WI 53718). The NDA is submitted electronically, as a 505(b)(2) application. The Chemical Type is 5 (New Formulation or New Manufacturer, Same or New Indication). It is a duplicate of a drug product [Sodium Pertechnetate Tc 99m Injection USP] produced by another manufacturer [Northstar] with same active moiety, same salt form, [Na^+][$^{99m}TcO_4^-$], same dosage form and the same indication. Date of submission was January 1, 2013; the company contact is Scott D. Moffat, Vice President of Regulatory Affairs & Quality. The PDUFA goal date is November 4, 2013.

2. Background

The story of the Technetium Generator is very lengthy. But, the short of it is that the design of the currently marketed technetium generators are based on the original invention at Brookhaven National Laboratories (1957). It became available in 1960 from BNL, but did not become commercially available until 1964. During its early use in nuclear medicine (1960's – mid 1970's), ^{99}Mo for use in the generator was produced by neutron irradiation of ^{98}Mo targets in a nuclear reactor, following the nuclear reaction [$^{98(42+56)}_{42}Mo + {}^{1}_{0}n \rightarrow {}^{99(42+57)}_{42}Mo + \gamma$]. With a neutron capture cross-section of only 0.15 barns, the efficiency of the conversion to ^{99}Mo is low, with most of the stable

nuclei remaining unconverted. Hence, the ^{99}Mo produced by this process [**$^{98}Mo(n, \gamma)^{99}Mo$**] has a relatively low specific activity, compared to that by current methodology, fission [$^{235}U(n, f)^{99}Mo$]. Low specific activity ^{99}Mo, as used in the early technetium generators, required large columns, packed with large quantities of alumina (aluminum oxide). As a result, the generators were large and unwieldy for use in nuclear pharmacies. Moreover, with the large columns, the $^{99m}TcO_4^-$ (formed from nuclear decay of adsorbed $^{99}MoO_4^{2-}$) had to move with saline elution through a large volume of alumina to the column exit. That resulted in $^{99m}TcO_4^-$ in a relatively large saline volume, leading to a low $^{99m}TcO_4^-$ concentration. Meantime, the integration of gamma cameras with computers had been making changes in how images are acquired, an innovation that paved the way for more comprehensive imaging technologies utilizing ^{99m}Tc, including dynamic flow studies. But, the achievement of maximal advantages of these technologies required high concentrations of $^{99m}TcO_4^-$, and that was severely hindered by technetium generators manufactured with low specific activity ^{99}Mo. A better method had to be found for production of the ^{99}Mo. Thus, the switch was made from the (n, γ) process to that of fission [$^{235}U(n, f)^{99}Mo$] utilizing the nuclear reaction:

$$[^{235}_{92}U + ^{1}_{0}n \rightarrow ^{236}_{92}U \rightarrow {}^{A[82\ldots.100]}_{Z}X + {}^{A[128\ldots.150]}_{Z}X \rightarrow \textbf{(purifications)} \rightarrow {}^{99}_{42}Mo]$$

With this change came the first practical, commercial technetium generators, and the two generators that currently remain marketed in the U.S. are UltraTechnekow (Covidian/Mallinckrodt, approved by the FDA on 11/16/1973) and Technelite (Lantheus, approved on 11/16/1976). The larger neutron capture cross-section (37 barns) for fission, compared to that (0.15 barns) of the (n, γ) reaction made possible ^{99}Mo with the requisite specific activity to fully utilize the benefits of the ideal radionuclide (^{99m}Tc) in nuclear medicine. However, the downside of the fission process is the relatively arduous purifications necessary, and the technical / engineering problems in running and maintaining nuclear reactors dedicated to production of high specific activity ^{99}Mo.

Initially, there were 3 commercial suppliers of HEU (Nordion-NRU reactor-AECL, Ottawa, Canada; Union Carbide-Cintichem New York, 1966; General Electric, CA). The last two of these suppliers were relatively quickly discontinued (1990 and 1977, respectively). In later years, there were added other suppliers of $^{99}MoO_4^{2-}$ (Petten HFR, Netherlands; IRE, Belgium; NTP, South Africa; Maria reactor, Poland; REZ reactor, Czechoslovakia; OPAL reactor, ANSTO-Australia), utilizing nuclear reactors operating with HEU / LEU fuel. But, in recent years, there have been recurrent shortages of fission ^{99}Mo, caused by aging nuclear reactors and the consequent shutdowns to make repairs to comply with safety regulations. Exacerbating this problem has been the absence of a U.S. source of ^{99}Mo, with all supplies coming from Europe, resulting in the encumbrance of the supply line to the U.S. In turn, that impacts patient care, since at least 80% of all nuclear medicine procedure involves ^{99m}Tc.

In the currently-approved technetium generators, the method of separation of $^{99m}TcO_4^-$ from $^{99}MoO_4^{2-}$ is with an alumina column. In this method, $^{99}MoO_4^{2-}$ is retained by alumina, but $^{99m}TcO_4^-$ is not; so the latter comes off the column into the eluate during elution of the generator. The specific activity of the $^{99}MoO_4^{2-}$ adsorbed to the alumina must be high (large amount of ^{99}Mo radioactivity in a small mass of molybdate) so as to

achieve a highly concentrated solution of $^{99m}TcO_4^-$ in the eluate coming off the column. That has forced the use of fission ^{99}Mo, and thus perpetuates our dependence on European sources. NorthStar came to the FDA with a proposed new version of the technetium generator, one that can use low specific activity ^{99}Mo. Their version of the generator employs a radically different method of separation of $^{99m}TcO_4^-$ from $^{99}MoO_4^{2-}$. That would allow for a switch, back to a non-fission process [$^{98}Mo(n, \gamma)^{99}Mo$] that can be used in this country, while at the same time create a generator that can produce $^{99m}TcO_4^-$ with very high radioactive concentration.

The fundamental principle of TechneGen is a reverse in the order of selectivity of the column material, so that rather than $^{99}MoO_4^{2-}$ retained on the column, as in the conventional technetium generator, it is $^{99m}TcO_4^-$ that is retained. This change in the selectivity allows the $^{99m}TcO_4^-$ to be concentrated on the column, with repetitious loading of recovered $^{99}MoO_4^{2-}/^{99m}TcO_4^-$ solution, and so not to render the strength of the $^{99m}TcO_4^-$ product dependent on the specific activity of the ^{99}Mo /$^{99}MoO_4^{2-}$. As a consequence, TechneGen will be capable of producing $^{99m}TcO_4^-$ in a strength at least matching that from conventional technetium generators, but requiring the use of low specific activity ^{99}Mo / $^{99}MoO_4^{2-}$ in their manufacture. The technology critical to TechneGen is the ABEC column. ABEC is a PEG form, chemically bonded to styrene-divinylbenzene resin bead. It presents an unusual order of selectivity, and does not work by typical ion-exchange mechanisms; I have discussed this in IQA-N202158el#1095. As this is beyond the scope of this CDTL review, the reader is referred to the IQA.

In this method, the mass of $^{99}MoO_4^{2-}$ applied to the ABEC column is non-consequential, since it is not retained by ABEC, the only dependence being how much capacity ABEC has for $^{99m}TcO_4^-$. The $^{99m}TcO_4^-$ is effectively concentrated on the ABEC column. The capacity for how much mass of $^{99m}TcO_4^-$ can be retained on ABEC has not been fully characterized, but appears to be substantial. ABEC concentration of $^{99m}TcO_4^-$ is a process that is none other than chromatography, by mechanisms not fully understood. However, it is subject to the same fundamental factors in chromatography theory. Band size and band shape are fundamental to separation outcome, and I will discuss this later under "How the TechneGen Generator Works." Although ABEC does not appear to be particularly prominent in the history of radiochemical chromatography, it has an apparent successful history of use at DOE's Hanford site for removing long-lived ^{99}Tc from the Hanford Tank waste liquids. What is in the NDA is as much as we know about ABEC, presumably due to information being otherwise classified.

The objectives of NorthStar are to use TechneGen firstly with low specific activity ^{99}Mo, obtained from the previous isotope production method, $^{98}Mo(n, \gamma)^{99}Mo$. Later, NorthStar intends to ^{99}Mo from the newer accelerator process [$^{100}Mo(\gamma, n)^{99}Mo$]. Accelerator ^{99}Mo will also be of low specific activity, and potentially represent another supply line of this critical medical isotope for meeting the nuclear medicine needs in the U.S. The concept in TechneGen is novel, in light of the science and technology of radionuclide generators, and it could represent a milestone in their history. In theory, it could potentially help to rectify the shortage situations due to aging nuclear reactions (European) that have been the only suitable source of ^{99}Mo up to this point. In the

$^{98}Mo(n, \gamma)^{99}Mo$ process, the nuclear fuel that will be used to produce the requisite thermal neutrons is LEU. From this standpoint, TechneGen could also aid in achieving the mandate of conversion from HEU to LEU.

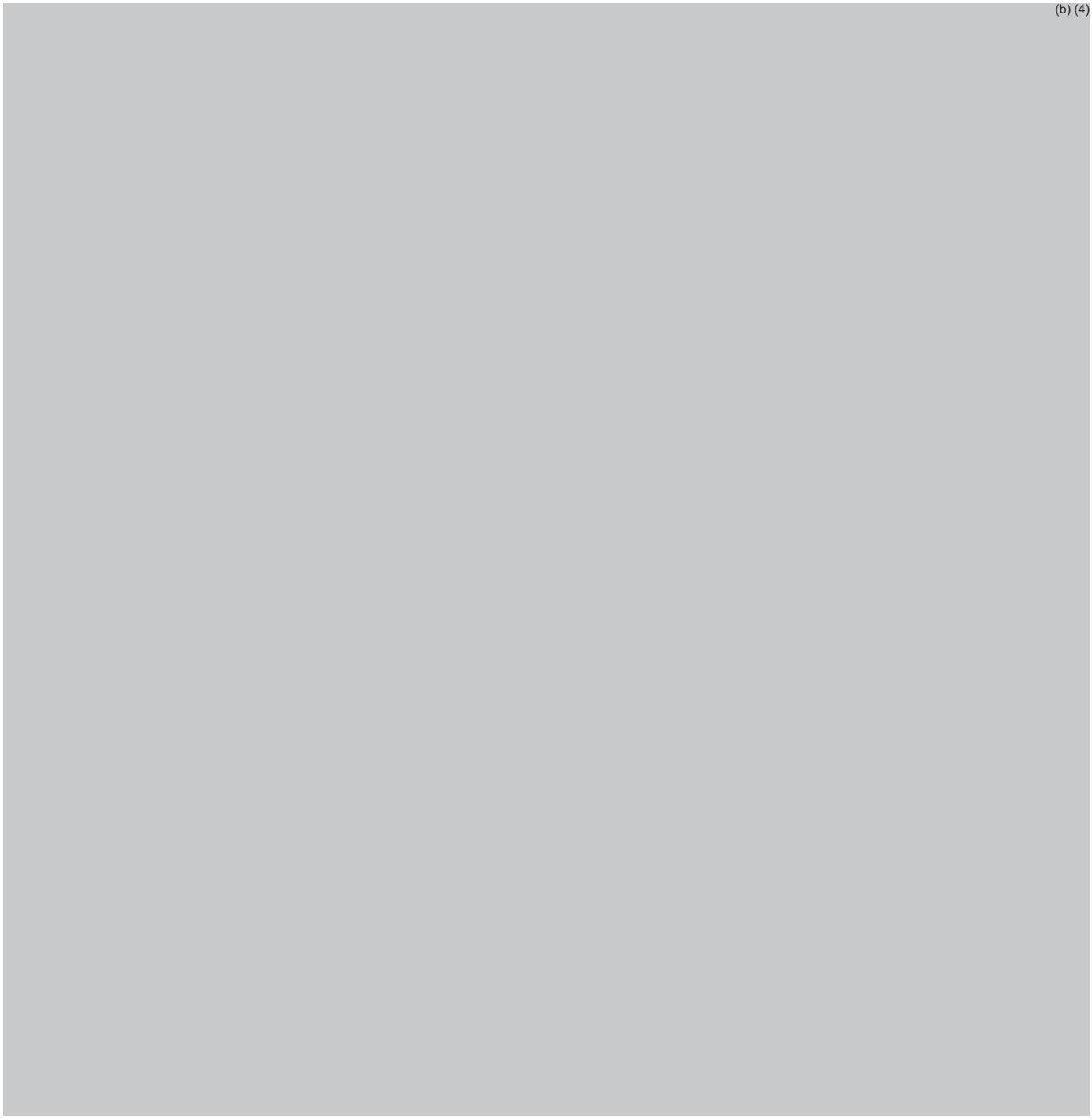
3. TechneGen Generator

The TechneGen Generator System consists of (1) a "generator," seen in the following picture (the module in the center, with open doors), and (2) computer (seen to the right of the generator). I am showing a flow map below a picture of the generator / computer, including a correlation with a flow diagram tracing the fluid pathway and what happens during operation of the generator.

unclear whether the design as described in the NDA (above depiction) is that actually intended for marketing; hence, what is shown in this CDTL review may only be representative. At the date of this CDTL, we do not know the answer to this question, and it is so noted by the primary CMC reviewer in the DMF review under separate cover (NorthStar's DMF 26592). The reader is referred to the CMC review of DMF 26592, relating to the technical details in the design and operation of TechneGen, including the computer controls and software.

How the TechneGen Generator Works:

(b) (4)



4. Product Composition from TechneGen Generator

A. Drug Substance:

The drug substance is the same, **Na ^{99m}TcO$_4$**, as in the currently approved technetium generators, and as discussed in the NDA, it meets the purity / quality standards in the current USP monograph.

B. Drug Product:

The Drug Product is Sodium Pertechnetate Tc99m Injection and has the following composition (Table 1, reproduced from the NDA):

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

Component	Concentration (mCi/mL)	Amount per Vial (Elution)	Function

(b) (4)

4. Chemistry, Manufacturing and Controls Issues

The primary CMC reviewer (Ravi Kasliwal, Ph.D., Chemistry Reviewer, ONDQA, DNDQA III / Branch VII) identified a list of substantive issues that were communicated to NorthStar in a teleconference on July 23, 2013 and is included in the Primary Review (October 7, 2013). The most prominent of these issues can be divided into 5 major areas, as shown below.

(1) **Optimization of flow rates**:

(a) (b) (4)

(b) Optimization of (b) (4) the ABEC column.

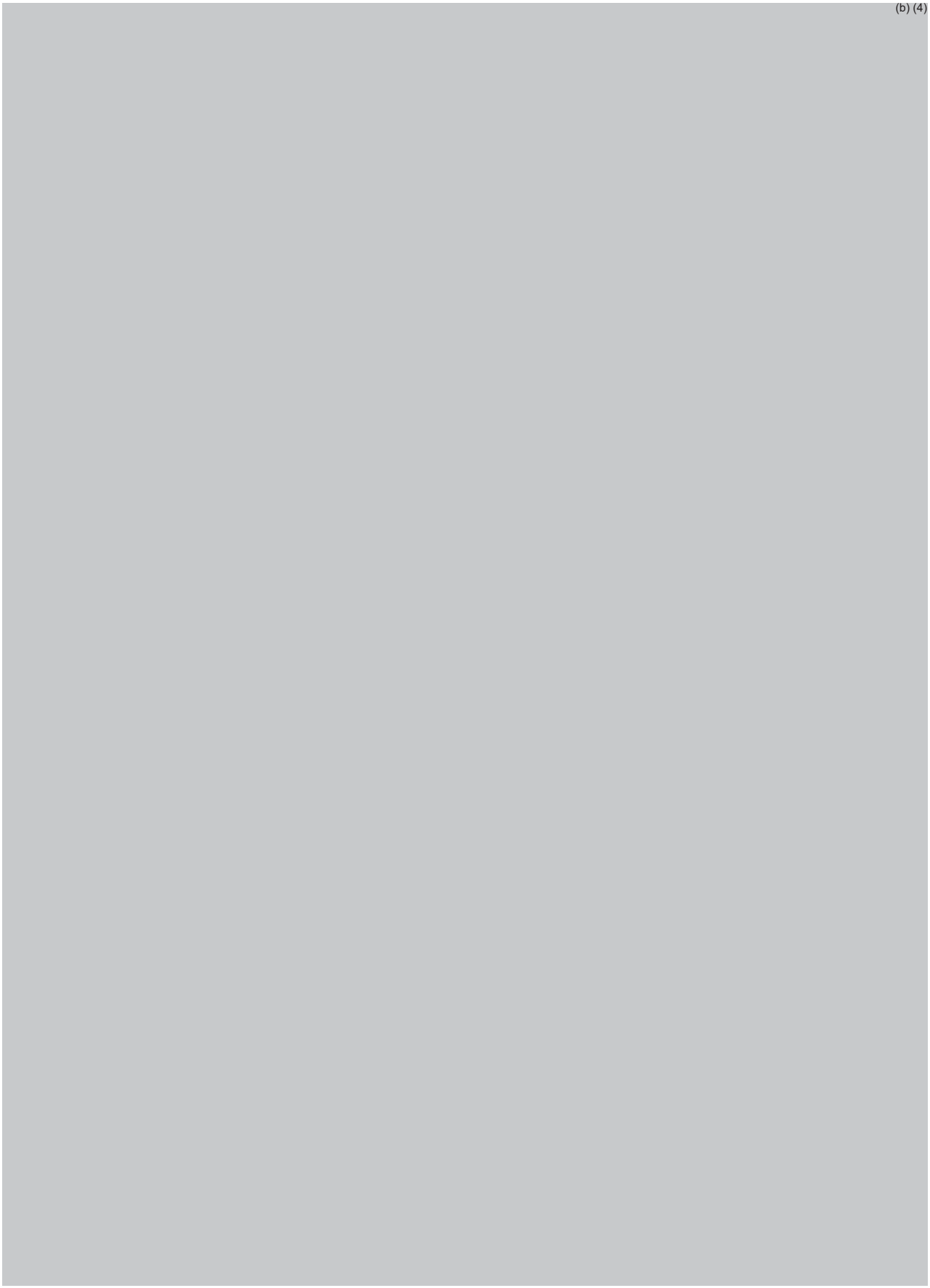
(c) Optimization of (b) (4) ABEC (b) (4)

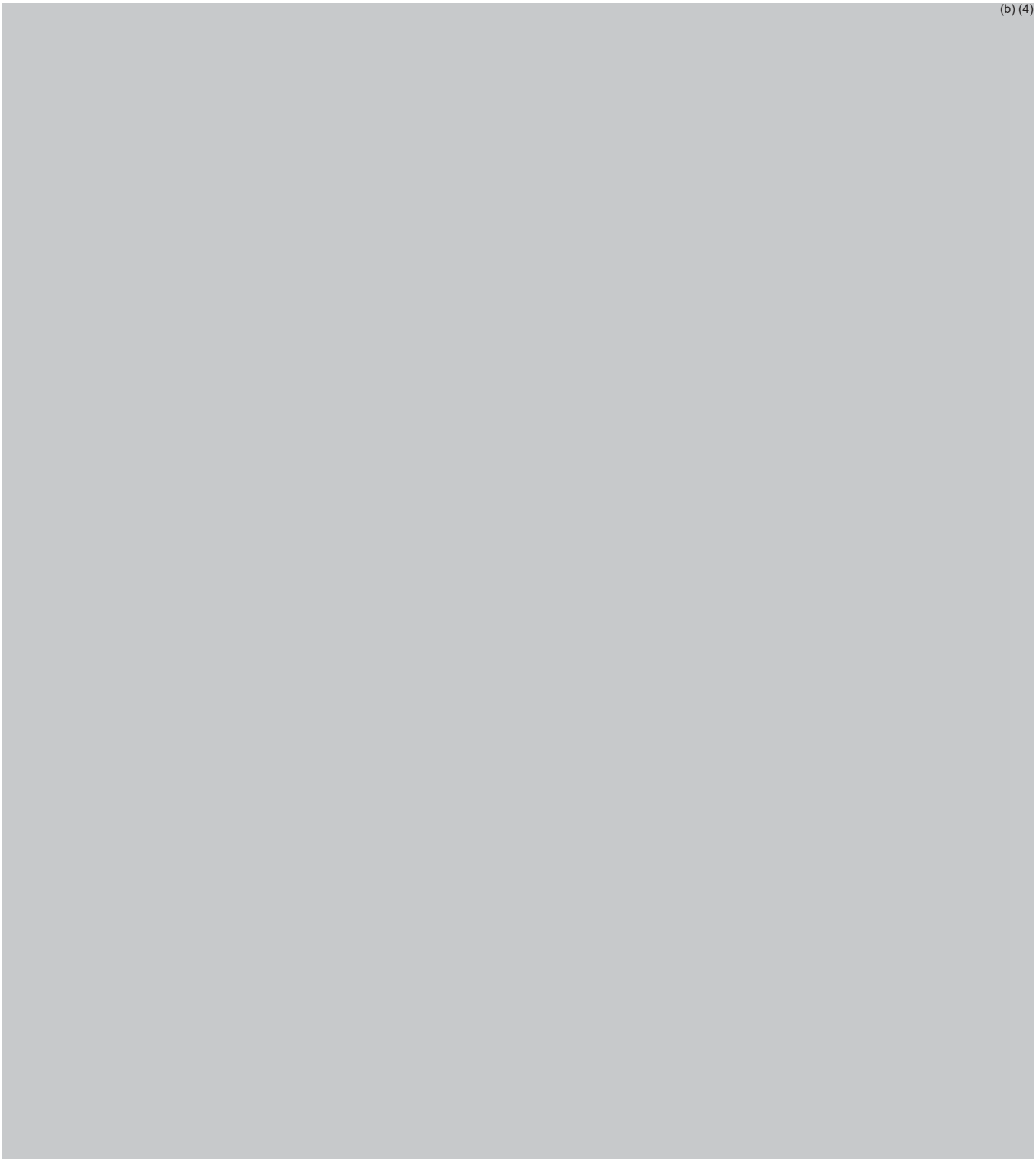
These optimizations correspond to the Steps in the operation of the TechneGen Generator that I have discussed in Part 3 (How the TechneGen Generator Works) on the preceding page. There is also a step (b) (4)

[redacted] (b) (4) Hence, successful optimization of flow rates cannot be overemphasized, and what is wanting in this application is an understanding of how these optimized flow rates are assured and maintained. This is going to be critical for a system that is going to be used in what is representative of real world use.

(2) **ABEC column** [redacted] (b) (4) For any radionuclide generator, the **separation column** is the "guts" of the generator, because if it does not live up to its fundamental function, it does not matter what the remaining processes are in operating the generator. The consequences of a faulty generator column includes (a) the most grievous of all, a potential breakthrough of the parent radionuclide into the generator eluate, or (b) a low concentration of the radionuclide product. In TechneGen, the [redacted] (b) (4) But, any propensity for instability has not been characterized by NorthStar, and is part of the issues for controls on the manufacture of the ABEC column.

(3) **Specifications for $\underline{K_2{}^{99}MoO_4}$.**
ABEC serves the purpose to concentrate the $^{99m}TcO_4^-$; [redacted] (b) (4) as I have already discussed. But, there is also the issue of what radionuclidic impurities are contained in the $K_2{}^{99}MoO_4$, what would not be retained and go with it into the recovery vessel, and what might be retained and go into the $^{99m}TcO_4^-$ during saline elution. The radionuclidic impurity profile of $K_2{}^{99}MoO_4$ would come from two sources, the first (a) of which is that generated from the other isotopes in naturally-occurring Mo (^{92}Mo, ^{100}Mo, ^{94}Mo, ^{95}Mo, ^{96}Mo, ^{97}Mo) [redacted] (b) (4) . The second (b) source would come from other metal impurities in the naturally-occurring Mo that would also undergo [redacted] (b) (4) neutron bombardment.


(b) (4)



(4) **TechneGen Generator Performance**. The issues (primary CMC review) include the need for data demonstrating the capability of (b) (4) ((b) (4) to manufacture the generator, and it is not clear regards the final version of the software that will be used in the computer control. Also, at the time of submission of the NDA, it was noted that (b) (4) had not as yet

manufactured a complete TechneGen generator. This is important, because it is related to **generator performance**, and also translates to the necessity that [redacted] be inspected (as I discuss under Section 5, Manufacturing Sites), because **otherwise it cannot be assured** that generators manufactured in the [redacted] facilities will produce a product meeting the established specifications for Sodium Pertechnetate Tc 99m Injection (USP).

(5) **Reagents, Reagent Kits and other Equipment**. In addition to these 4 major CMC areas, there are some issues regards the [redacted] packaged in [redacted] vials (stability, expiration date, labels) and the **Auxiliary equipment** (Reagent Kit, Cleaning Kit, Collection Kit). The composition of the Kits are described in both the NDA and DMF 26592, but there is limited information provided on the manufacturers of the components, specifications and controls, and expiration dates (as ascertained by the primary reviewer, Ravi Kasliwal). Also, there are issues regards the **containers** ($K_2{}^{99}MoO_4$ recovery; reagent solutions), and others. Finally, there is the issue of **manufacturing sites**.

5. Manufacturing Sites

(1) **OC Acceptable Recommendations**

- [redacted] (performs analytical testing – chemical and microbiological) – OC acceptable ([redacted])
- [redacted] (performs [redacted] of packaged [redacted] – OC acceptable [redacted])

(2) **Pending Sites**

- MURR, University of Missouri Research Reactor Center (production of $K_2{}^{99}MoO_4$ – irradiation of molybdenum targets, [redacted] and release of Potassium Molybdate Mo 99 Solution) – March 18, 2013

MURR had received an acceptable facility decision on the basis of profile (March 18, 2013). However, the dispensing equipment has not yet been completely installed - will be ready for inspection after 11/21/2013. It is not clear at this point what was the rationale for the "acceptable on the basis of profile," and it appears to CMC (primary reviewer and myself) that these facilities for processing and dispensing of the $K_2{}^{99}MoO_4$ should be inspected.

(3) **Sites Not Ready for Inspection (at time of NDA primary review)**

- NorthStar (primary and secondary cartridge filling and packaging; source vessel assembly and vessel recovery for ^{99}M dispensing; Reagent Kit packaging; microbiology and monograph testing in support of the NDA) – determined to be ready 9/30/2013, and has been assigned an inspection (10/08/2013).
- [redacted] (**build and test commercial TechneGen**) – will not be ready until [redacted].

There has been discussion of whether [redacted] should be inspected. But, it must be remembered that TechneGen is a "radionuclide generator," and by definition [21 CFR

315.2] is a drug product. The precedent for regulating radionuclide generators as drugs is the statute [21 CFR 310.3(n)], as it has been applied to other radionuclide generators (UltraTechnekow, Technelite, and Cardiogen-82). Without inspection, there is no way to assure that (b) (4) can manufacture the generator. The following comment was sent to NorthStar: "*We note that the commercial TechneGen Generator will be manufactured by* (b) (4) *in* (b) (4) *We also note that* (b) (4) *has not manufactured the entire TechneGen generator in the past. Provide information and data that this company is capable of manufacturing the generator*" (Ravi Kasliwal, primary review, 10/07/2013).

- (b) (4) (formulates, fills, sterilizes packages and labels Reagent Solutions used in the elution of TechneGen; performs analytical and microbiological testing of in association with reagent solutions; performs batch release testing of Reagent Solutions).

There is a Withhold recommendation (b) (4)) for (b) (4). OC has indicated that (b) (4) are not operating under 21 CFR 211. Complicating this issue at this time (10/11/2013) is the uncertainty of whether NorthStar will change this manufacturer. NorthStar was asked about this, and was informed (reference to primary CMC review, 10/07/2013) that any change would require complete CMC information, including stability, of the solution intended for such changes.

6. Microbiology Product Quality Issues

The microbiology review was performed by Jessica Cole, Ph.D. (Microbiology Reviewer, CDER/OPS, September 30, 2013). Microbiology is recommending Approvable Pending response to microbiology deficiencies. This is based on an assessment of the risk, which they deem to be high for producing a product that is not sterile. TechneGen is a complicated system, which contrasts with the currently approved technetium generators that are closed systems, sterile when shipped and are used for only 2 weeks, then shipped back to the manufacturer (or appropriate receiving facility handling such products). As well, there is a minimum amount of USER-manipulation with the conventional technetium generators.

The view from microbiology is that TechneGen is a "miniature, mobile aseptic processing facility." From Jessica Cole's review, "traditional aseptic processing practices mitigate the risk to patients through implementation of current good manufacturing practices, which include extensive validation studies, training programs, and regulatory oversight in the form of routine onsite inspections. This generator system will be used outside of the normal aseptic manufacturing paradigm."

To highlight the microbiology deficiencies, (a) certain of the transfer fluid lines pose a risk for microbial contamination and are a source of bioburden and endotoxin – among the sterile equipment that is used in traditional aseptic manufacturing processes includes product transfer lines. The data from NorthStar does not support their claim that the cleaning protocol is adequate to remove bioburden from the system. (b) Non-sterile manufacturing processes rely on the sterilizing filters for patient safety, but NorthStar does not propose to test the filters for integrity after use, and there will be no processing simulations (media fill studies) performed by the end user at the final installation site,

contrary to the requirements of CGMP's and USP <797>. As well, NorthStar provides no supporting justification for the lack of media fill studies. Other microbiology deficiencies (c) are described, and include such matters as lack of process validation, validation of the (b) (4) sterilization, peroxide (3%) cleaning validation studies, as well as several deficiencies regarding the lack of tests for whether the final dosage form meets the proposed specifications. A complete list of deficiencies and their discussion is found in the Microbiology Review.

7. Consults

CDRH:

On May 22, 2013, CDRH presented slides with preliminary comments, based on their review (as requested by ONDQA) of DMF 26592. A formal review by CDRH (Prasanna Hariharan, September 24, 2013) earmarked the following issues:

(a) **Lack of pressure / flow monitoring and sensor controls.**
NorthStar indicated that "the system does have a sensor [of parent and daughter fluid flow], and if the radiation conditions were altered, the system has (or will have) the capability to shut down or alert the operator." In response to NorthStar's comment on the sensor controls and software, FDA stated that the process sounds like a decision tree, and requested that NorthStar submit the decision tree describing it in detail. The FDA is waiting for this information.

(b) **Potential kinking of tubing**.
This amounts to partial occlusion of flow lines, and is particularly relevant to tubing lines located outside the instrument, since they are not being shielded and thus present a safety concern.

(c) **Effect of fluid flow rate.**
NorthStar has indicated that product yield does not change even after (b) (4) the flow rates. They also state that a (b) (4) flow rate does not affect the generator performance, (b) (4). To the latter, CDRH is requesting that NorthStar provide scientific justification.

(d) **Effect of malfunctioning valves**.
CDRH is saying in their review that failure of the valves could have consequences impacting safety (e.g., leaking of radioactive fluids) and thereby affect the efficacy of elution that could in turn affect product quality. Hence, CDRH is requesting NorthStar to simulate the effect of malfunctioning valves (e.g., valve fails to open, valve fails closing).

(e) **Potential for incomplete cleaning**.
CDRH is requesting NorthStar to provide the flow rates (minimum, maximum, average) through each valve and generator column (e.g., ABEC and alumina).

CDRH (Software):

During an internal meeting held on September 18, 2013 there was a discussion with the software review component in CDRH (Joseph Jorgens III) . They divide the software review issues into three classifications: Minor, Moderate and Major. CDRH indicated in this meeting that they had discussed the software considerations with the clinical discipline in DMIP, and had come to the conclusion (from the CDRH perspective) that the issues were in the Moderate classification. The clinical opinion, voiced at the September 18 meeting was from Philip Davis, MD of DMIP, who concluded that they had no concerns from the standpoint of patient harm if there were such a software failure.

In their formal review of the software (Joseph Jorgens, September 24, 2013), the following information is being requested of NorthSar – to provide:

(a) A Moderate Level of Concern
(b) Information on the programming language, hardware platform, operating system (if applicable) and the use of Off-The-Shelf software
(c) A description of the clinical hazards presented by the device and its products, causes and severity of the hazards, methods of control of the hazards and testing done to verify implementation of controls, and any residual hazards
(d) Software requirements specifications (Traceability Matrix, etc.)
(e) Architecture design chart (functional units, software modules, flow diagrams, etc.)
(f) Software design specifications
(g) Traceability analysis – traceability among hazards, specifications and their mitigation
(h) Verification and validation documentation
(i) Revision history (log of software revisions during development – major / minor changes
(k) Unresolved anomalies (bugs, defects)
(l) Run-time error (tools used to detect run-time errors, error type the tool detects, method of applying these tools and summary report, and conclusion)

HUMAN FACTORS STUDY:

A Human Factors Study was jointly requested by ONDQA and DMIP to assess the impact to the product by the many more steps required of the operator of TechneGen, compared to that for the conventional technetium generator. The Human Factors Study is expected of the sponsor of the NDA for TechneGen. The Protocol Assessment of NorthStar's HFS was performed (July 9, 2013) by Barbara Cohen, Social Sciences Analyst of the following FDA address: OMPT/CDER/OND/ODDEIV/DNCE. The following is a summary of what I consider are the major points made in the **TechneGen Human Factors Social Science Review** – NorthStar should provide:

(a) A document discussing the critical hazards that could result from incorrect use of TechneGen
(b) Steps and scenarios for the human factors study – in so doing, NorthStar should consider direct observation in the real world environment, and employ the typical user groups that would be involved in operation / use of TechneGen
(c) HFS should include testing under simulated conditions

(d) Metrics to be used (pH, ^{99}Mo breakthrough, specific activity, acceptable bioburden following use, etc.)

DMIP has provided additional comments that are part of the review, and focuses on the critical hazards that could result from incorrect use of TechneGen (identification of the worst case – catastrophic failure, and would include the asking of such questions as how they might occur, how likely they are to occur, what are the possible consequences of each, and how might they be prevented). It was pointed out to NorthStar that they should engage the use of a highly experienced human factors testing firm that possesses specific expertise in engineering of medical imaging products that are similar to TechneGen.

8. Clinical

The clinical review was performed by Phillip Davis, MD (Medical Officer, OND/ODEIV/DMIP), September 18, 2013. Highlights in the clinical review include multiple deficiencies in labeling that relates to instructions for the preparation and safe use of TechneGen. This labeling refers to the USER's manual and training materials. The deficiencies identified in these labeling materials remain outstanding in the opinion of the clinical team, and prevents them from being able to complete an appropriate review of TechneGen prescribing information. Based on these deficiencies, the clinical reviewer is recommending a Complete Response for the current review cycle.

9. USER's Manual

The assessment of the User Manual by the clinical team has already been duly noted. The problematical state of the User's Manual has also been recognized by the other members of the review team. To summarize, the manual in its current state is complicated to follow. Instructions on how to operate the generator are interwoven with too much discussion of theory and principles, leaving the review team with the sense that users in typical nuclear pharmacies would be overwhelmed with information, although important, are not of immediate necessity for the operation of the generator. Due to its complicated nature, the operation of TechneGen will require substantial attention to detail to avert improper use. Although the discussions on theory and principles provide important perspectives on the reasons for the various operations, it would be better placed in, e.g., appendixes, where a user could refer for a more in-depth understanding. There needs to be a section in the **User Manual with unencumbered directions for how to operate the generator.** The consensus on this is unanimous on the part of all review disciplines. Hence, there will need to be substantial revision of the User's Manual, and NorthStar has been made aware of this.

10. Interdisciplinary Assessments and Overall Conclusions:

All review disciplines have the same general assessment – that TechneGen is not ready at this time for entering the real world. Rather than being fully developed at the time of submission of the NDA, it has been undergoing development by NorthStar during our review, and reviewers have been serving in the capacity of providing guidance to NorthStar in those regards. To some extent, this is no different than for most radiopharmaceutical NDA's. In the case here, it is particularly prominent. However, it

must be understood that there were exceptional circumstances existent with this NDA, along with forward thinking about critical future needs that led to its special consideration, and these have been discussed in various internal meetings. But, in retrospect, the full extent of the problems in the NorthStar NDA were not understood, and some of the problems did not surface until the NDA was reviewed in greater depth, including some issues with some of the manufacturing sites leading to their not being ready for inspection.

Despite these problems, the innovative concept in TechneGen presents a worthy review enterprise, due to (a) the habitual shortage crises we face with the production of fission ^{99}Mo (aging nuclear fission reactors) to continue to meet technetium generator needs in the U.S., (b) it's exacerbation by the absence of a U.S. source of generator-suitable ^{99}Mo, and (c) the looming specter that is ahead of us – the mandate that HEU be replaced with LEU. ^{99m}Tc continues to be the workhorse in nuclear medicine, due to its ideal gamma photon of 140 KeV and half-life of 6 hours. It is evident that ^{99m}Tc will remain pivotal in the performance of nuclear medicine procedures. Potentially, TechneGen offers obvious solutions to the issues that I have briefly discussed if the deficiencies in the NDA for TechneGen can be satisfactorily resolved. There are numerous CMC deficiencies (Primary Review, Ravi Kasliwal, Ph.D., 10/07/2013). But, we believe that these deficiencies are resolvable. Much of the body of interdisciplinary deficiencies are the result of the fact that TechneGen presents a technetium generator far more complicated than the ones currently in use, and thus requires a greater level of user-attention and manipulation.

One of the by-products of the complicated nature of TechneGen is the need for clear directions on how to use the generator. The entire review team recognizes this, and the first and second pass on the User Manual has demonstrated that it is wanting for substantial revision to make for safe use of TechneGen, and I have discussed some of the more prominent issues in the User Manual under Section 9 of this CDTL review.

To summarize for an overall conclusion, we can surely say that at this point there is not enough in place to be assured that TechneGen is a robust technetium generator and can be used safely by typical nuclear pharmacy personnel to produce product meeting established specifications for Sodium Pertechnetate Tc99m Injection, USP. Much needs to be done by NorthStar to address the numerous deficiencies that have been identified. However, on the plus side, the deficiencies for CMC are fully resolvable in my opinion, with CDRH to follow suit. The User manual is well within the capability of being revised, so that there is a clear direction on how the generator is to be used. What remains at some issue are the deficiencies identified by the microbiology team, and that will essentially rest with NorthStar to address, (b) (4)

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

/s/

ELDON E LEUTZINGER
10/11/2013

DANAE D CHRISTODOULOU
10/11/2013