

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202158Orig1s000**

**CLINICAL REVIEW(S)**

## NDA Clinical Review Memorandum

Update to NDA Review dated 9/18/2013

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NDA:	202158
Drug Name:	RadioGenix System (previously called TechneGen Generator System)
Sponsor:	NorthStar Medical Radioisotopes, LLC
Submission Date:	5/07/2017 (Resubmission/Class 2) FDA SD#21
Reviewer:	Phillip B. Davis, MD
Team Leader:	Nushin Todd

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### I. Executive Summary

In the 5/07/2017 NDA Class 2 resubmission for RadioGenix (new technology Tc99m generator), the sponsor addressed all deficiencies noted in my Clinical Review filed 9/18/2013 in DARRTS including completion of the human factors protocol and revision of the operator's guide (and user training) and PI to allow safe use of the RadioGenix System.

**The Clinical Team recommends approval of this innovative (non-Uranium sourced starting material) Tc99m generator system.**

### II. Background

NDA 202158 is a 505(b) (2) application for the RadioGenix System, a new technology generator for producing Tc99m Injection; the application consists of CMC and nonclinical information. Financial disclosures were not required due to no clinical studies being conducted.

The RadioGenix System is a computer monitored and controlled automated synthesis module used to prepare Sodium Pertechnetate Tc99m Injection using non-Uranium sourced, low specific activity Potassium Molybdate Mo99 solution as starting material. RadioGenix utilizes proprietary technology for separation of daughter Tc99m from its Mo99 parent, and concentrates the Tc99m. Sodium Pertechnetate Tc99m Injection is used in the preparation of FDA approved diagnostic radiopharmaceuticals.

NorthStar submitted a 505(b)(2) application on 1/04/2013 for NDA 202158. On 3/18/2013, the sponsor received a filing communication from DMIP that contained comments regarding the human factors validation protocol and operator manual. On 3/19/2013, DMEPA provided comments to NorthStar about the human factors protocol; a Complete Response (CR) was sent to the sponsor on 11/04/2013 for clinical and product quality issues.

Since the CR letter was sent, DMEPA has managed the review of the sponsor's human factors protocol testing with consultative input from CDRH. Dr. Michelle Fedowitz (DMIP Associate Director for Labeling) has managed revision of the PI for the RadioGenix system. I agree with the team's assessment that this novel combination product is now approvable.

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/s/  
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PHILLIP B DAVIS  
01/26/2018

NUSHIN F TODD  
01/29/2018

## Clinical Review of 505(b)(2) NDA Submission

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**NDA** 202158  
**Product:** TechneGen Generator System  
(Sodium Pertechnetate Tc99m Injection)  
**Sponsor:** NorthStar Medical Radioisotopes, LLC (NorthStar)  
**Submission:** New 505(b)(2) NDA  
**Submission Date:** 1/04/2013  
**PDUFA Date:** 11/042013

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### I. Executive Summary

During the course of our multi-discipline review of the TechneGen NDA, the clinical team identified multiple deficiencies in the labeling (user's manual, training materials), related to instructions for preparation and safe use of the Technegen system. These deficiencies remain outstanding and have prevented the clinical team from being able to complete an appropriate review of the Technegen prescribing information.

**Based on outstanding deficiencies in the product labeling, the clinical reviewer recommends a complete response for the current review cycle.**

### II. Background

NDA 202158 is a 505(b) (2) application for TechneGen, a generator system for producing Tc99m Injection. This application consists mostly of CMC and nonclinical information; the clinical team is providing review and guidance regarding the proposed labeling. The TechneGen Generator System is a computer monitored and controlled automated synthesis module used to prepare Sodium Pertechnetate Tc99m Injection using low specific activity Potassium Molybdate Mo99 Solution as Starting Material. The TechneGen System utilizes proprietary technology for separation of daughter Tc99m from its Mo99 parent, and also concentrates the Tc99m.

In the primary review filed 5/27/2013, the clinical reviewer provided recommendations regarding the indications and dosing and administrations sections of the proposed drug label. Among others, these recommendations included deleting "Placenta Localization", edits to the "Brain Imaging" and "Blood Pool Imaging" indications, and edits to the dosage section of the label.

During subsequent cross discipline discussions and review of the application, the clinical team identified deficiencies in the labeling, including the training materials and, user's

manual . A list of major deficiencies were sent to the sponsor in the 3/18/2013 *filing issues identified* document, and these were again discussed with NorthStar during the 7/17/2013 and 7/23/2013 teleconferences between FDA and representatives from NorthStar Medical Radioisotopes. This review addendum is being filed to highlight the outstanding deficiencies in the sponsor's proposed labeling and provide an overall recommendation for the current review cycle.

### III. Issues

#### **Operations Manual, User Training and Human Factors Validation Protocol**

In the 3/18/2013 *Filing Issues Identified* document, FDA noted that the sponsor had not sufficiently developed plans for implementation and use of the Technegen system at clinical facilities. The review team determined both the operations manual and human factors engineering/usability report needed substantial revision in order for the Agency to complete a review of the NDA. The operations manual was noted to be unclear with regards to multiple terms and general organization. FDA recommend NorthStar develop a systematic process for training end users. Additionally, we reiterated the need to perform a human factors assessment study to determine the sufficiency of the sponsor's user manual and training program, once fully developed.

NorthStar developed an updated and reorganized operations manual and revised human factors validation protocol, which was the subject of a teleconference between FDA and the sponsor on 7/17/2013. Upon review of the meeting package NorthStar submitted for the teleconference, FDA noted that the sponsor was still developing the Technegen generator system, as the meeting documents referred to both generation 1 and generation 2 Technegen systems. Therefore, FDA provided feedback on the revised documents in order to provide guidance to the sponsor for further development of the user guides.

The operations manual was noted to be too lengthy and not logically organized. FDA recommended the document be revised into more of a "how to" type document that concisely outlines the entire process for using the system, and that it also contain information on corrective actions for generator malfunction or user error. The Agency also stated "Prior to finalizing the human factors protocols, please develop 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 where an error could occur". Regarding the human factors validation protocol, the sponsor stated it was developed according to the FDA Guidance Document "Applying Human Factors and Usability Engineering to Optimize Medical Device Design, June 22, 2011". However, the review team noted that the proposed validation protocol needed substantial revisions including, but not limited to, the following:

- Inclusion of 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.

- Conduction of 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.
- Inclusion of stand-alone testing of the user’s manual in a segment of trained users.
- Performance of some testing under conditions of time pressure, continued interruptions and/or poor lighting.
- Inclusion of metrics that are objective, and quantifiable, as well as subjective ones.
- Inclusion of an estimate of sample size that incorporates the factors studied.

NorthStar generally agreed to the FDA recommendations regarding the operations manual, user training and human factors validation protocol. One point of disagreement was that the sponsor stated the “Design of Technegen is complete”; FDA does not agree with this assertion as the product labeling is still under development. At the present time, NorthStar has not submitted the above mentioned labeling documents with the discussed and agreed upon revisions.

#### **IV. Reviewer Comments**

The clinical reviewer notes that after the operator’s manual has again been revised and the human factors protocol finalized and executed, data obtained from completion of the protocol will likely lead to changes in the Technegen labeling, including the operator’s manual. Therefore, as previously mentioned, the labeling for Technegen is still very much *in development*. In conclusion, the Technegen NDA submission lacks sufficient information for FDA to fully evaluate the safe use of this Tc-99m generator.

**Reviewed by:**  
***Phillip Davis, MD***  
Medical Officer

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/s/  
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PHILLIP B DAVIS  
09/18/2013

LIBERO L MARZELLA  
09/18/2013

I concur with Dr. Davis' assessment and recommendation for regulatory action

## Clinical Review of 505(b)(2) NDA Submission

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**NDA** 202158  
**Product:** TechneGen™ Generator System  
(Sodium Pertechnetate Tc99m Injection )  
**Sponsor:** NorthStar Medical Radioisotopes, LLC (NorthStar)  
**Submission:** New 505b2 NDA  
**Submission Date:** 1/04/2013  
**PDUFA Date:** 7/03/2013

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### I. Background

The sponsor has submitted a 505(b) (2) application for TechneGen, a unique generator system for producing Tc99m Injection. This application consists mostly of CMC and nonclinical information; the clinical team is providing comment and guidance regarding the proposed indications and dosing and administration sections of the drug label.

The TechneGen Generator System is a computer monitored and controlled automated synthesis module used to prepare Sodium Pertechnetate Tc99m Injection using low specific activity Potassium Molybdate Mo99 Solution as Starting Material. The TechneGen System utilizes unique technology for separation of daughter Tc99m from its Mo99 parent, and also concentrates the Tc99m. The sponsor states these two key features permit the use of low specific activity Mo99 produced by non-fission processes, and also the preparation of high concentration Tc99m solutions.

The sponsor proposes the following label 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 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.

We note the sponsor's proposed indications closely resemble those in the Ultra-Technekow DTE (NDA 017243), Technelite (NDA 017771), and the GE Tech Generator (NDA 17693 – new submission at Agency) drug labels. However, the field of diagnostic imaging has greatly evolved in the past several decades and some of these indication

statements may need revision and/or removal from the drug label. We conducted a review of professional society guidelines related to nuclear medicine imaging to evaluate support in the clinical community for each indication proposed by the sponsor. Guidelines evaluated included those of the Society of Nuclear Medicine and Molecular Imaging (SNMMI), American Society of Nuclear Cardiology (ASNC), American College of Radiology (ACR).

## II. Review Indications

The clinical team conducted a review of relevant professional society guidelines for nuclear medicine imaging as related to the sponsor’s proposed indications. The reviewer also leans on personal experience in nuclear medicine practice combined with relevant brief literature searches to make recommendations presented in the below table. Please see the appendix in section IV for a visual representation of the reviewer’s recommendations.

Indication (Dosing)	Supported by Professional Guidelines?	Reviewer Comments	Recommendation
Brain Imaging including Cerebral radionuclide angiography (10 to 20 mCi)	No	Brain perfusion scans and brain death scans are described in the guidelines <sup>1,2</sup> using kit based radiotracers; recommended radiotracers include Tc-99m ECD, Tc-99m HMPAO, and Tc-99m DTPA.	Remove the “cerebral radionuclide angiography” text. The “brain imaging” text <u>could be edited to say “Brain Imaging with reagent kits”</u> or similar wording.
Placenta Localization (1 to 3 mCi)	No	The reviewer believes this is an outdated indication for Tc-99m pertechnetate use. Ultrasound is the modality of choice; MRI and CT are also use.	Remove indication.  <i>*Indication is removed in most current submitted version of label.</i>
Blood Pool	No	SNMMI & ASNC	<u>Remove the</u>

<p>Imaging including radionuclide angiography. (10 to 30 mCi)</p>		<p>Guidelines <sup>1,3</sup> describe “First-Pass Radionuclide Angiography”. However, the reviewer notes this is uncommonly performed in clinical practice and Tc-99m pertechnetate <u>is not</u> the recommended agent, Tc-99m labeled red blood cells (RBCs) are used. The reviewer also notes “blood pool imaging” is a generic term that can be applied to infection imaging using nuclear techniques with kit based tracers, as well as gated equilibrium radionuclide ventriculography using Tc-99m labeled RBCs.</p>	<p>“radionuclide angiography” text. The “blood pool” imaging indication <u>could be edited</u> to say “Blood Pool Imaging with reagent kits” or similar wording.</p>
<p>Urinary Bladder Imaging (0.5 to 1 mCi)</p>	<p>Yes</p>	<p>Guidelines <sup>1,2</sup> describe direct and indirect radionuclide cystography for the evaluation of vesicoureteral reflux using Tc-99m pertechnetate.</p>	<p>No action necessary.</p>
<p>Thyroid Imaging (1 to 10 mCi)</p>	<p>Yes</p>	<p>This indication is supported by guidelines<sup>1,2</sup>, literature and decades of clinical use.</p>	<p>No action necessary.</p>
<p>Salivary Gland Imaging (1 to 5 mCi)</p>	<p>Yes</p>	<p>SNM 2010 Guidelines describe salivary gland imaging</p>	<p>No action necessary.</p>
<p>Nasolacrimal</p>	<p>No</p>	<p>There is no</p>	<p>No action necessary.</p>

Drainage System Imaging (100 µCi)		professional society guideline support for this indication. However, the reviewer notes this is a procedure that is described in recent literature <sup>4</sup> and textbooks <sup>5</sup> .	
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\* Please note the recommended label doses seen in the above table were compared to current clinical practice guidelines and found to be consistent with SNM recommendations.

### Reviewer’s Comments

*The reviewer notes the regulatory challenges encountered when attempting to edit the approved Tc-99m generator labels without submitted clinical data to base our decisions upon. The above recommendations are based on clinical judgment and current clinical practice; the reviewer acknowledges these recommendations may fall outside what is achievable within our regulatory framework in the context of no clinical data submitted with this application. The reviewer’s opinion is that it’s debatable as to whether “brain imaging” and “blood pool imaging” should be either edited or deleted. The reviewer believes the “placenta localization” indication is the most outdated in the label and is appropriate for deletion, as placenta imaging is not performed in the practice of medicine today with either Tc-99m alone or with Tc-99m based kit reagents.*

## Specific Label Sections

### Section 2.2

#### Dosage

The following text is found:

Sodium Pertechnetate Tc99m is usually administered by intravenous injection but can also be given orally or be instilled directly into the eye or urinary bladder.

If the oral route is elected, the patient should fast for at least six (6) hours before and two (2) hours after administration.

#### Comments/Recommendation

*The reviewer notes that gastroesophageal emptying studies are commonly performed in the nuclear medicine department to evaluate for gastric motor function and for signs of reflux and aspiration. However, the most commonly used and recommended radiopharmaceutical for this procedure is Tc-99 labeled sulfur colloid. The reviewer does not believe that Sodium Pertechnetate Tc99m is used alone (that is, not bound to sulfur colloid) for this procedure.*

Excerpt from: Procedure Guideline for Adult Solid-Meal Gastric-Emptying Study 3.0\* (approved by SNM 2/08/2009)

“2. Meal preparation:

a. Mix 18.5–37 MBq (0.5–1 mCi) of <sup>99m</sup>Tc-sulfur colloid into the liquid egg whites.”

The reviewer recommends either:

- a. *delete the text regarding oral administration, or*
- b. *revising the text to more accurately state:*

“Sodium Pertechnetate Tc99m is usually administered by intravenous injection, but can also be given orally **when labeled with sulfur colloid** or be instilled directly into the eye or urinary bladder.

### Section 2.9

Excerpt from section 2.9, see yellow highlight:

**Table 1 Absorbed Radiation Doses from Intravenous Injection (PEDIATRIC)**

Tissue	37 MBq (1 mCi) Dose		185 MBq (5 mCi) Dose	
	mGys	rads	mGys	rads
Thyroid (without perchlorate)	46.0	4.60	230.0	23.0
Thyroid (with perchlorate)	9.7	0.97	48.5	4.85
Large Bowel (with perchlorate)	19.0	1.90	95.5	9.55
Testes	1.0	0.10	5.1	0.51
Ovaries	2.2	0.22	11.0	1.10
Total Body	1.5	0.15	7.6	0.76

<sup>2</sup> Conway, J.J., et al., Direct and indirect radionuclide cystography. J. Urol. 113:689-693, **May 1975.**

#### *Comment/Recommendation*

*The reviewer notes references for the radiation dosimetry estimates (both adult and pediatric) are from the 1970s. It may be useful to ask the sponsor to perform a literature search for up to date references for estimating absorbed radiation doses for adult and pediatric patients for the given label indications. We appreciate input from our medical physicist colleagues on this issue.*

### Section 5.2

#### **Cumulative Radiation Exposure**

Sodium Pertechnetate Tc99m injection, <sup>(b) (4)</sup>, contributes to a patient’s overall long-term cumulative radiation exposure. **Long-term cumulative radiation exposure is associated with an increased risk of cancer.** Use the lowest dose of sodium pertechnetate Tc99m necessary for imaging and ensure safe handling to protect the patient and health care worker [see Dosage and Administration (2.2) and (2.3)]. <sup>(b) (4)</sup>

#### *Comment/Recommendation*

The above text is in the proposed label for TechneGen in section 5.2. However, the reviewer does not see similar text in the Ultra-TechneKow® DTE (NDA 17243) label that relates overall long-term cumulative radiation exposure to increased risk of cancer. If missing from the Ultra-TechneKow label (and other Tc-99m generators), this text

should be added for consistency sake and to avoid any unfair marketing implications for those sponsors of previously approved Tc-99m generators.

### **Section 6.1**

#### **Postmarketing Experience**

(b) (4)

#### *Comment/Recommendation*

The above text is in the proposed label for TechneGen in section 6.1. Again, the reviewer does not see similar text in the Ultra-TechneKow® DTE (NDA 17243) label; this text should be added to the other Tc-99m generator labels if missing.

### **Section 8.3**

#### **Nursing Mothers**

Technetium Tc99m is excreted in human milk during lactation; therefore, formula-feedings should be substituted for breast-feedings. (b) (4)

#### *Comment/Recommendation*

The above text is in the proposed label for TechneGen in section 6.1. The reviewer does not see the yellow highlighted text in the Ultra-TechneKow® DTE (NDA 17243) label; we should probably remove this text from the TechneGen label or recommend this text in our labeling supplement request (on clinical matters) for the other tech generators, listed below. We appreciate input from our PMHS colleagues on this issue.

#### Current Approved Tc-99m generators.

NDA 17243 (Mallinckrodt/Covidean, Ultratechnekow)

NDA 17771 (Lantheus, Technelite)

#### Also:

NDA 17693 (GE Healthcare) – Previously approved, then discontinued, now with new supplement submitted to Agency)

### **III. References:**

The following professional society guidelines were referenced in order to make the recommendations in this review. Multiple guidelines were referenced from the SNMMI and ACR, the below 2 links to specific ASNC guidelines were also used.

1. Society of Nuclear Medicine and Molecular Imaging (SNMMI)  
Practice Guidelines

<http://interactive.snm.org/index.cfm?PageID=772>

2. American College of Radiology (ACR)

<http://www.acr.org/Quality-Safety/Standards-Guidelines/Practice-Guidelines-by-Modality/Nuclear-Medicine>

3. American Society of Nuclear Cardiology (ASNC)

<http://www.asnc.org/imageuploads/ImagingGuidelinesFPRNA020509.pdf>

<http://www.asnc.org/imageuploads/ImagingGuidelineERNA.pdf>

4. Seminars in Ophthalmology. Update on imaging of the lacrimal drainage system, 2012, Sep-Nov; 27(5-6): 175-86.

5. MacDonald, Anita, Burrell, Steven. Infrequently Performed Studies in Nuclear Medicine: Part 1. September 2008, Vol. 36, no. 3: 132-143.

#### **IV. Appendix**

The below excerpts from the label are edited to better visualize the recommendations in this review. Yellow highlighted text represents recommended additional text.

#### **Highlights of Prescribing Information**



Reviewed by:  
*Phillip Davis, MD*

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/s/  
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PHILLIP B DAVIS  
05/27/2013

## Clinical Review of 505(b)(2) NDA Submission

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**NDA** 202158  
**Product:** TechneGen™ Generator System  
(Sodium Pertechnetate Tc99m Injection )  
**Sponsor:** NorthStar Medical Radioisotopes, LLC (NorthStar)  
**Submission:** New 505b2 NDA  
**Submission Date:** 1/04/2013  
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Imaging including radionuclide angiography. (10 to 30 mCi)		Guidelines <sup>1,3</sup> describe “First-Pass Radionuclide Angiography”. However, the reviewer notes this is uncommonly performed in clinical practice and Tc-99m pertechnetate <u>is not</u> the recommended agent, Tc-99m labeled red blood cells (RBCs) are used. The reviewer also notes “blood pool imaging” is a generic term that can be applied to infection imaging using nuclear techniques with kit based tracers, as well as gated equilibrium radionuclide ventriculography using Tc-99m labeled RBCs.	“radionuclide angiography” text. The “blood pool” imaging indication <u>could be edited</u> to say “Blood Pool Imaging with reagent kits” or similar wording.
Urinary Bladder Imaging (0.5 to 1 mCi)	Yes	Guidelines <sup>1,2</sup> describe direct and indirect radionuclide cystography for the evaluation of vesicoureteral reflux using Tc-99m pertechnetate.	No action necessary.
Thyroid Imaging (1 to 10 mCi)	Yes	This indication is supported by guidelines <sup>1,2</sup> , literature and decades of clinical use.	No action necessary.
Salivary Gland Imaging (1 to 5 mCi)	Yes	SNM 2010 Guidelines describe salivary gland imaging	No action necessary.
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## Specific Label Sections

### Section 2.2

#### Dosage

The following text is found:

Sodium Pertechnetate Tc99m is usually administered by intravenous injection but can also be given orally (b) (4).

If the oral route is elected, the patient should fast for at least six (6) hours before and two (2) hours after administration.

#### Comments/Recommendation

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“2. Meal preparation:

a. Mix 18.5–37 MBq (0.5–1 mCi) of <sup>99m</sup>Tc-sulfur colloid into the liquid egg whites.”

The reviewer recommends either:

a. *delete* the text regarding oral administration, *or*

b. *revising* the text to more accurately state:

“Sodium Pertechnetate Tc<sup>99m</sup> is usually administered by intravenous injection, but can also be given orally **when labeled with sulfur colloid** or be instilled directly into the eye or urinary bladder.

### Section 2.9

Excerpt from section 2.9, see yellow highlight:

**Table 1 Absorbed Radiation Doses from Intravenous Injection (PEDIATRIC)**

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(b) (4)

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**Section 6.1**  
**Postmarketing Experience**

(b) (4)

*Comment/Recommendation*

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**Section 8.3**  
**Nursing Mothers**

Technetium Tc99m is excreted in human milk during lactation; therefore, formula-feedings should be substituted for breast-feedings. (b) (4)

*Comment/Recommendation*

The above text is in the proposed label for TechneGen in section 6.1. The reviewer does not see the yellow highlighted text in the Ultra-TechneKow® DTE (NDA 17243) label; we should probably remove this text from the TechneGen label or recommend this text in our labeling supplement request (on clinical matters) for the other tech generators, listed below. We appreciate input from our PMHS colleagues on this issue.

Current Approved Tc-99m generators.

NDA 17243 (Mallinckrodt/Covidean, Ultratechnekow)  
NDA 17771 (Lantheus, Technelite)

Also:

NDA 17693 (GE Healthcare) – Previously approved, then discontinued, now with new supplement submitted to Agency)

**III. References:**

The following professional society guidelines were referenced in order to make the recommendations in this review. Multiple guidelines were referenced from the SNMMI and ACR, the below 2 links to specific ASNC guidelines were also used.

1. Society of Nuclear Medicine and Molecular Imaging (SNMMI)  
Practice Guidelines

<http://interactive.snm.org/index.cfm?PageID=772>

2. American College of Radiology (ACR)

<http://www.acr.org/Quality-Safety/Standards-Guidelines/Practice-Guidelines-by-Modality/Nuclear-Medicine>

3. American Society of Nuclear Cardiology (ASNC)

<http://www.asnc.org/imageuploads/ImagingGuidelinesFPRNA020509.pdf>

<http://www.asnc.org/imageuploads/ImagingGuidelineERNA.pdf>

4. Seminars in Ophthalmology. Update on imaging of the lacrimal drainage system, 2012, Sep-Nov; 27(5-6): 175-86.

5. MacDonald, Anita, Burrell, Steven. Infrequently Performed Studies in Nuclear Medicine: Part 1. September 2008, Vol. 36, no. 3: 132-143.

#### **IV. Appendix**

The below excerpts from the label are edited to better visualize the recommendations in this review. Yellow highlighted text represents recommended additional text.

#### **Highlights of Prescribing Information**



Reviewed by:  
*Phillip Davis, MD*

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/s/  
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PHILLIP B DAVIS  
04/04/2013

## **Medical Officer's Review of Operations Manual and Human Factors Assessment**

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**NDA:** 202-158

**Sponsor:** Northstar Medical Radioisotopes

**Today's date:** March 8, 2013

**Reviewer:** Dwaine Rieves, MD/DMIP

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During a recent team meeting, I volunteered to try to find review staff who could review two documents supplied within the NDA:

-Operations Manual

-Human Factors Assessment

I contacted reviewers within the Center for Devices and Radiological Health (CDRH) and, as of this date, have been unable to find any reviewers with the expertise sufficient to perform detailed review of the Manual.

Regarding the Manual, as Ms. Carol Benson (CDRH) noted, "I sent your request to our office managers in OIR including the Division of Radiological Health. No one in our office has experience in reviewing these devices. You may need a radiation chemist. However, we do not know of any."

Regarding the Human Factors Assessment, Dr. Barbara Cohen (of CDER/ODE-IV) noted the following: "The testing that is referenced in this document has more to do, I think, with risk/hazard analysis and verification/validation - perhaps standard software/engineering testing paradigms but not necessarily defined universally as "human factors". As a side note, the testing that they do discuss was with 11 subjects - and seven of them were employees of the Sponsor. This is not the sort of independent customer analysis that we consider to be rigorous." We will send a consult to Dr. Cohen, once the Human Factors Assessment is better defined by the company.

I further examined the Manual and Human Factors Assessment and am impressed at the lack of clarity within the documents. Indeed, the documents (and end user process) appear to need considerable more development. I have drafted a few comments for the review team to consider as we work to propose some comments for the company. I reiterate these comments below.

Draft of Proposed Comments to Northstar:

We have identified problems within the TechneGen System Operation Manual and the Human Factors Engineering/Usability Report. Both documents appear to need substantial revision in order for us to complete the review. We encourage you to initiate a redevelopment of both of these documents to address the following items:

Regarding the Operation Manual:

1. Clarify the (b) (4) and develop a training program and re-evaluation program for the end users. Specifically, we encourage you to develop a systematic process that consists

of a program for training an (b) (4) (perhaps using a certification approach) and designating this individual(s) by a unique identifier (such as a “Certified User”). The training program should consist of instructional materials, testing and a plan for periodic retesting to ensure the end-user is properly operating the system. Submit these materials for our review. Additionally, we anticipate that you will need to perform a human factors assessment study to determine the sufficiency of the training program.

- a. The Manual currently says the system must be (b) (4). What does this mean? Are you trying to say that only licensed nuclear pharmacists are to operate the system? Who are the (b) (4)
- b. You must include a glossary of terms and use these terms consistently throughout the manual. Currently, multiple terms appear to refer to the same system components. For example, what is “the instrument:” (b) (4) “cartridges:” “disposables;” (b) (4) “(b) (4);” “RSO:” “fault.”
- c. Describe the components of the system upfront in the Manual, including identification of the “disposables.”
- d. Is the computer supplied with the system? Is it possible to add other applications to this computer? Why does the manual say, (b) (4) Does this mean other applications may be added to the computer ad hoc?
- e. Where is the system to be placed? Page 5 says, (b) (4) The Manual needs to clarify the acceptable locations for the entire system and further define the location for any components of the system that must be disconnected and moved to another location (such as a (b) (4)).
- f. Why is it mandatory that the cleaning protocol be run a minimum of every (b) (4) days? Since this is the “minimum,” are you actually saying it should be run more often? What controls are to be performed to assess the sufficiency of this cleaning process?
- g. The figures need revision to clarify unidentified acronyms and undefined components—such as “PSC;” and “transfer vessel.”
- h. Page 11—what is a “protocol” when you say, (b) (4)
- i. Page 19—What is a “fault” when you say, (b) (4)

- j. These two preceding sentences exemplify the current manual's lack of user-friendliness.
- k. The manual must be thoroughly redeveloped to explain the system in a user-friendly manner that describes components consistently and avoids complex technical terms as well as terms of no relevance to the end user.

Regarding the Human Factors Report:

- 2. The supplied document appears to represent a risk/hazard analysis and limited validation testing, largely performed by company experts.
  - a. You appear not to have developed a training program (with materials) sufficient to actually perform an end user human factors assessment. Once you have developed this program (including redevelopment of the Operations Manual), we encourage you to propose a Human Factors Test that actually assesses the sufficiency of the training program and the Operations Manual.
  - b. The supplied operations testing appears to have included company experts; hence, the information provides very limited information to assess the ultimate use of TechneGen by representative end users.

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/s/  
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RAFEL D RIEVES  
03/08/2013