

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202158Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Deferral of Risk Evaluation and Mitigation Strategies (REMS) Review**

Date: September 26, 2013

Reviewer(s): Bob Pratt, Pharm.D.  
Division of Risk Management

Team Leader: Cynthia LaCivita, Pharm.D.  
Division of Risk Management

Drug Name(s): TechneGen Generator System for preparation of Sodium  
Pertechnetate Tc<sup>99m</sup> Injection

Therapeutic Class: Diagnostic Radiopharmaceutical

Dosage and Route: Various dosages  
Intravenous, oral, and instillation

Application Type/Number: NDA 202158

Applicant/sponsor: NorthStar Medical Radioisotopes

OSE RCM #: 2013-642

## 1. INTRODUCTION

This document is to defer comment on whether a risk evaluation and mitigation strategy (REMS) is needed for the TechneGen Generator System for preparation of Sodium Pertechnetate Tc<sup>99m</sup> Injection. On January 4, 2013, NorthStar Medical Radioisotopes submitted a 505(b)(2) New Drug Application (NDA) seeking approval of the TechneGen system for various proposed diagnostic imaging indications. TechneGen is a unique manufacturing system for the production of Sodium Pertechnetate <sup>99m</sup>Tc Injection. The applicant did not submit a proposed REMS or risk management plan.

### 1.1. BACKGROUND<sup>1-4</sup>

Metastable technetium-99 (<sup>99m</sup>Tc) is the medical isotope of choice for diagnostic nuclear imaging. Approximately 25 million imaging procedures were carried out with <sup>99m</sup>Tc radiopharmaceuticals worldwide in 2008. The isotope is available using the parent isotope <sup>99</sup>Mo (which undergoes beta decay to <sup>99m</sup>Tc) in conventional generator systems such as Ultra-TechneKow™ DTE and TechneLite®. Conventional generators load high specific activity <sup>99</sup>Mo as molybdate (<sup>99</sup>MoO<sub>4</sub><sup>2-</sup>) onto an alumina chromatography column. Washing the column with a saline solution elutes the <sup>99m</sup>Tc daughter isotope as pertechnetate (<sup>99m</sup>TcO<sub>4</sub><sup>-</sup>) while molybdate remains adsorbed on the column. The <sup>99m</sup>Tc is formulated into various radiopharmaceutical complexes using FDA-approved technetium kits and then administered to patients for specific imaging procedures.

The primary process for producing <sup>99</sup>Mo with high specific activity is through the fission of enriched uranium in a nuclear reactor. There are no domestic reactors in the U.S. that produce <sup>99</sup>Mo from enriched uranium, and only several foreign producers are approved to import the product into the U.S. In recent years, ongoing maintenance issues with some of the foreign reactors have resulted in shutdowns that caused supply interruptions of <sup>99</sup>Mo, shortages of <sup>99m</sup>Tc, and delays in performing imaging procedures.

<sup>99</sup>Mo can be produced without the use of enriched uranium by bombarding naturally occurring <sup>98</sup>Mo with neutrons in a nuclear reactor, or by photofission of naturally occurring <sup>100</sup>Mo using linear accelerator technology. These production methods are either currently available or under development in the U.S. However, these methods result in a <sup>99</sup>Mo product with low specific activity. The use of a conventional generator system with low specific activity <sup>99</sup>Mo is not practical, as it would require a large chromatography column and large elution volumes; in addition, all of the current <sup>99m</sup>Tc kits would need to be reformulated.

The TechneGen system has been developed as an alternative to conventional generator systems for the production of <sup>99m</sup>Tc. TechneGen is an automated multi-column manufacturing system that can use low specific activity <sup>99</sup>Mo. Use of the system could help relieve U.S. dependence on foreign sources of <sup>99</sup>Mo and drug shortages of <sup>99m</sup>Tc. In the TechneGen system, a solution of the

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<sup>1</sup> Bartholomä MD, et al. Technetium and gallium derived radiopharmaceuticals: Comparing and contrasting the chemistry of two important radiometals for the molecular imaging era. *Chem Rev* 2010;110:2903-2920.

<sup>2</sup> McAlister DR and Horwitz EP. Automated two column generator systems for medical radionuclides. *Appl Radiat Isot* 2009;67:1985-1991.

<sup>3</sup> Official Transcript of Proceedings, Nuclear Regulatory Commission. Advisory Committee on the Medical Uses of Isotopes, September 21, 2012 (accessible at: <http://pbadupws.nrc.gov/docs/ML1232/ML12324A220.pdf>).

<sup>4</sup> Technetium-99m Radiopharmaceuticals: Manufacture of Kits (Technical Reports Series 466). International Atomic Energy Agency. Vienna, 2008 (accessible at: [http://www-pub.iaea.org/MTCD/Publications/PDF/trs466\\_web.pdf](http://www-pub.iaea.org/MTCD/Publications/PDF/trs466_web.pdf)).

<sup>99</sup>Mo parent isotope is eluted through a primary separation chromatography column that binds <sup>99m</sup>Tc. The <sup>99m</sup>Tc is then stripped from the column and passed through an alumina purification column that binds any residual <sup>99</sup>Mo, allowing for the recovery of <sup>99m</sup>Tc at high purity in a small volume of solution.

TechneGen is designed to be a mobile, aseptic manufacturing system that consists of a <sup>99</sup>Mo solution container system, various syringe pumps, multiport valves, tubing and fluid lines, reagents, shielded chromatography columns, collection vials, filters, control electronics, and software. A simplified flow diagram of the system is shown in the Appendix. A nuclear pharmacist or technician, or possibly other personnel, will operate TechneGen in an unclassified pharmacy environment and be responsible for the following operations:

- Installation of reagent solutions and primary separation column
- Installation of the <sup>99</sup>Mo parent solution
- Aseptic assembly of the alumina column, sterilizing filters, and drug product collection vial, and installation of the product outlet station
- Entering required data into the computer and initiation of the elution process
- Removal of the <sup>99m</sup>Tc injection and performance of quality control testing
- Installation of reagent solutions and components required to perform weekly maintenance of a cleaning and sanitization cycle

The applicant has developed three guides (operator's manuals) that provide information for the TechneGen user. The "Operator Guide" contains information related to chemistry and design, operating parameters, user interface information, accessory kit summary information, and system storage; the "Controller Applications Guide" contains instructions for performing the Mo-Tc separation, initialization of the system, and the weekly cleaning protocol; and the "Accessory Kits and Mo99 Source Assembly Guide" provides instruction on aseptic assembly and installation.

## **2. MATERIALS REVIEWED**

- March 18, 2013, 74-Day Filing Communication
- April 4, 2013, DMF 26592, Section 9.3 Risk Management Summary
- April 4, 2013, Clinical Review
- May 15, 2013, Type C Meeting Package NDA 202158
- May 24, 2013, Microbiology Memorandum
- June 3, 2013, slides from NDA 202158 Mid-Cycle Meeting
- July 15, 2013, Social Science Review, TechneGen Human Factors Protocol and Operator's Manual
- July 29, 2013, Microbiology Memorandum
- September 9, 2013, slides from NDA 202158 Wrap-up Meeting

## **3. DISCUSSION**

In evaluating the need for a REMS, risks are considered in the context of the patient and not the user of the TechneGen system. The Nuclear Regulatory Commission (NRC) and its Agreement States license and regulate the possession and use of radioactive materials for nuclear medicine; these and other agencies have jurisdiction over occupational safety and health at licensed facilities.

The main risks to patients associated with the TechneGen system are potential product quality issues that include microbial and endotoxin contamination, radionuclide purity, chemical purity, pH of the preparation, and the administered dose of radioactivity. Although the USP publishes a Monograph for standards related to Sodium Pertechnetate Tc<sup>99m</sup> Injection, there will be no monograph testing of product generated by the TechneGen system at the user site.

The Microbiology review team has identified deficiencies with the TechneGen system's sterility assurance program, which is completely dependent on the sterilizing filters as well as the capacity of the user to aseptically manipulate and operate a complex manufacturing system. The cleaning and sanitization protocol has not been evaluated for bioburden reduction. There is also an undefined potential for bioburden issues associated with long-term storage of the system in an unclassified environment. Microbiology is recommending that the application receive a Complete Response due to these and other product quality deficiencies.

Quality control testing described in the TechneGen prescribing information will address risks related to radionuclide purity (<sup>99</sup>Mo breakthrough), chemical purity (aluminum breakthrough), and the administered dose of radiation activity. This testing is described in the labeling of the conventional generator systems, and NRC and State regulations address some of these risks as well. Testing of the preparation's pH will also be required and described in the prescribing information. However, the Chemistry review team is recommending that the application receive a Complete Response due to multiple chemistry, manufacturing and control deficiencies with the system.

Operation of the TechneGen system is complex and involves many more steps for the user compared with production of <sup>99m</sup>Tc using conventional generators. The applicant has proposed a training program for users that may include lectures, review of the user manuals, hands on demonstration, and assessment of participant performance on the operational tasks. Individuals successfully completing the training would receive certification of completion. The details of the training program have not been submitted to the NDA. The applicant submitted a Human Factors Study Plan to evaluate user performance and the need for revision of the training materials, but the Social Science review team found multiple deficiencies in the plan. Further evaluation of the operator manuals, training program, and human factors protocol is on hold until the applicant submits revised materials.

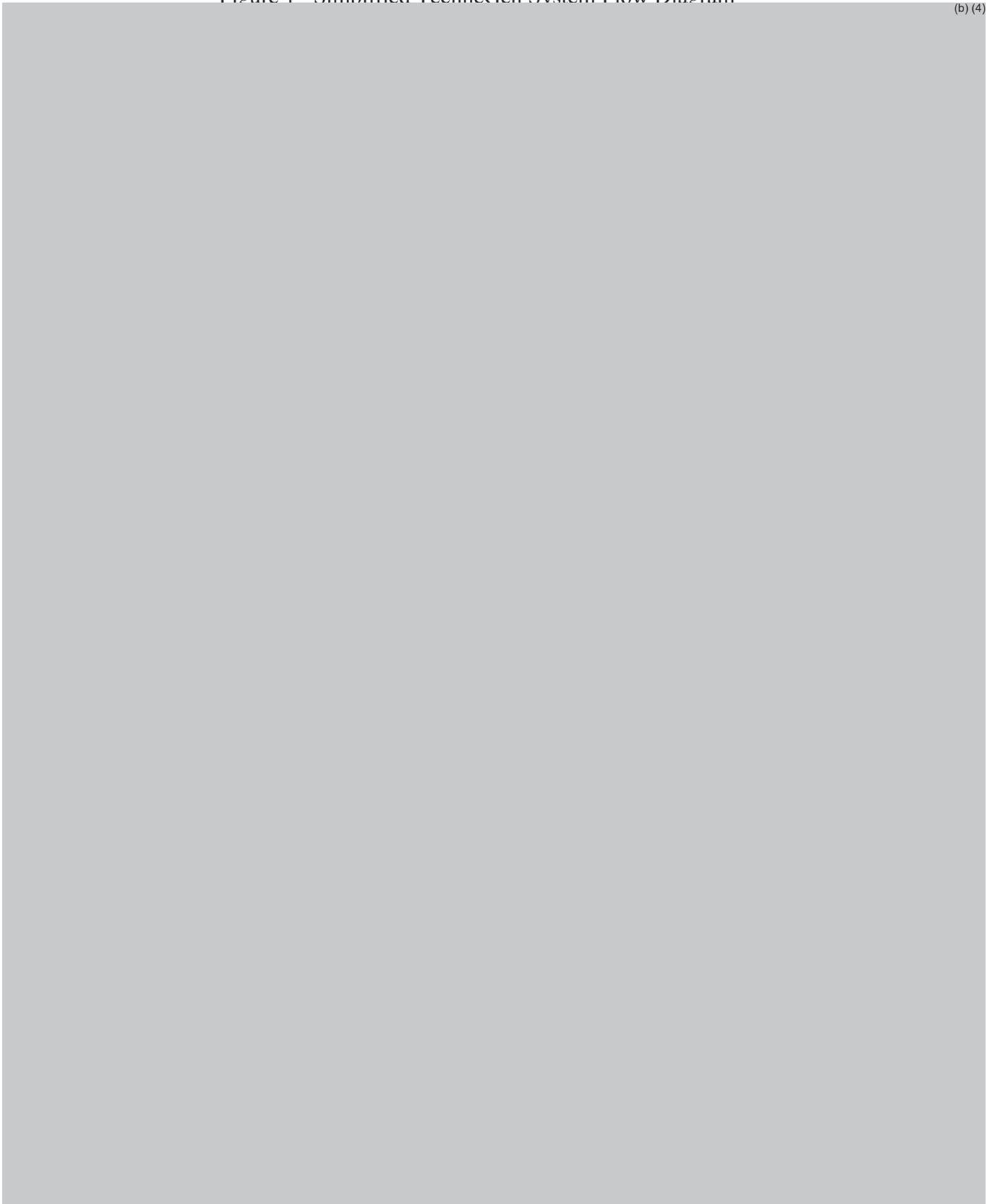
#### **4. CONCLUSION**

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

**APPENDIX**

Figure 1 Simplified TechneGen System Flow Diagram

(b) (4)



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/s/  
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09/26/2013

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09/27/2013