

**Mo-99 2013 TOPICAL MEETING ON
MOLYBDENUM-99 TECHNOLOGICAL DEVELOPMENT**

**April 1-5, 2013
Embassy Suites Downtown - Lakeshore
Chicago, Illinois**

**Use of LEU Produced Mo-99 in the Manufacture
of TechneLite® Generators**

Ira N. Goldman¹, Teresia Möller¹, Kathleen Mcfadden², Joseph Haepers¹

¹Manufacturing and Operations

²Sales and Marketing

Lantheus Medical Imaging, 331 Treble Cove Road, N. Billerica, MA 01862 USA

ABSTRACT

Lantheus Medical Imaging, Inc. (LMI) shipped the first commercial Low-Enriched Uranium (LEU) TechneLite® Generator on January 7, 2013. The LMI generator is the first Tc-99m generator in the U.S. that is manufactured using molybdenum-99 (Mo-99) produced from at least 95% LEU, which satisfies the new reimbursement requirements under the Center for Medicare and Medicaid Services (CMS) 2013 rules. In December 2011, LMI was the first U.S. manufacturer to receive FDA approval for the commercial use of LEU-sourced Mo-99 in the production of Tc-99m generators, and such generators have been routinely used for the past two years in the U.S. market. The qualification of LEU Mo-99 was done in close collaboration with NTP Radioisotopes (Pty) Ltd. (NTP) of South Africa and the Australian Nuclear Science and Technology Organization (ANSTO) over a 16 month period (Feb 2010-May 2011). The qualification tests and continued quality control (QC) testing of the commercial generators have demonstrated that the quality and properties of TechneLite® generators using LEU Mo-99 are equivalent to those manufactured using Mo-99 produced from Highly Enriched Uranium (HEU). This paper will describe Lantheus' process for the product addition of the LEU TechneLite® Generator, including the LMI manufacturing operations and steps that were carried out to facilitate the release and commercial sale of the LEU Tc-99m generator, as well as technical results on the comparison of the "LEU generator" to the "HEU generator".

INTRODUCTION

Routine commercial production and delivery of TechneLite[®] Tc-99m generators using molybdenum-99 (Mo-99) produced from Low Enriched Uranium (LEU) targets by Lantheus Medical Imaging (LMI) was begun in May 2011 (blended with Mo-99 produced from Highly Enriched Uranium (HEU targets). The qualification of LEU Mo-99 was performed in 2010-2011 in close collaboration with NTP Radioisotopes (Pty) Ltd. (NTP) of South Africa and the Australian Nuclear Science and Technology Organization (ANSTO) and this LEU Mo-99 meets the LMI Mo-99 specification based on the European Pharmacopeia Mo-99 monograph.

LMI has been providing completely LEU sourced (minimum 95% LEU content) generators for sale since January 7, 2013. These “all-LEU” TechneLite[®] Tc-99m generators are compliant with the Center for Medicare and Medicaid Services (CMS) \$10 add-on reimbursement payment for non-HEU produced Tc-99m doses, as part of the 2013 Hospital Outpatient Prospective Payment System (HOPPS).

LMI’s LEU and HEU-produced TechneLite[®] generators are equivalent in performance and use as recognized by FDA approval of LEU-produced Mo-99 generators. The only difference between the LEU TechneLite[®] generator and the standard TechneLite[®] generator is that LEU TechneLite[®] is produced using Mo-99 sourced from at least 95 percent LEU instead of HEU. The LEU TechneLite[®] generator has the same label and package insert as the standard TechneLite[®] generator. The differentiating feature is the visual identifier of a large, round green “dot” sticker on the top of the LEU TechneLite[®] generator can.

The LEU TechneLite[®] (Technetium Tc-99m Generator) is produced at LMI’s state-of-the-art manufacturing facility in Massachusetts. The LMI generator manufacturing line is semi-automated and includes steps for formulation of the Mo-99 solution, in-process determination of pH, Mo-99 batch activity concentration, Mo-99 breakthrough and generator column activity assay (on 100% of manufactured units). Quality control (QC) and release testing include testing of functional operation, eluate pH, chemical purity, radiochemical and radionuclidic purity, radionuclidic ID, Mo-99 breakthrough, sterility, and endotoxin levels at Date of Manufacture (DOM) to ensure the product quality is consistent and within specifications. The LMI Mo-99 specification for a qualified supplier is based on the European Pharmacopeia Mo-99 monograph.

Lantheus has an internal protocol which governs the process for the qualification of new Mo-99 suppliers and/or sources. In addition to this, per U.S. Food and Drug Administration (FDA) recommendation, three (3) independent qualification runs (no mixing of LEU and HEU Mo-99 sources) were performed on the LMI manufacturing line to qualify the LEU sourced Mo-99. Qualification testing of the generator units includes in addition to the routine QC and release testing, kit compatibility testing performed with anionic, cationic and neutral kits at time of initial elution (T₀) and expiry, microbiological testing (bacteriostasis and fungistasis), and testing of simulated customer elution samples at three (3) timepoints for assay of Mo-99 breakthrough, Tc-99m yield, pH and aluminum ion concentration.

RESULTS AND DISCUSSION

The TechneLite[®] generator provides Tc-99m as sodium pertechnetate USP drug product. The drug product is obtained by the aseptic elution of the generator column with sterile 0.9% saline and collected in a sterile, evacuated vial. During the commercial TechneLite[®] generator

production runs, 100% of the units are tested for Mo-99 breakthrough and column activity. The USP limit for Mo-99 breakthrough in the Tc-99m eluate at time of administration is 0.15 μCi Mo-99/mCi Tc-99m. The Mo-99 breakthrough level at product release (QC test) is significantly below the limit of $< 0.03 \mu\text{Ci}$ Mo-99/Tc-99m mCi (at time of elution), which indicates that upon customer elution, the Tc-99m material will be well below the USP 0.15 μCi specification (at least for 12 hours).

Commercial Manufacture of Tc-99m generator using LEU Mo-99

Beginning May 21, 2011, LMI purchased Mo-99 originating from HEU and LEU Mo-99 sources with an average ratio of 92%/8% in 2011 and 88%/12% in 2012, respectively. It is estimated that in the first quarter of 2013, LEU Mo-99 will account for approximately one third of LMI's Mo-99 purchases.

In 2011 and 2012, the TechneLite[®] generators were manufactured with LEU Mo-99, either as the sole source of Mo-99 or as blended with HEU Mo-99, and HEU Mo-99 as the sole source of Mo-99. The properties of these TechneLite[®] generators are equivalent to those manufactured using only HEU-produced Mo-99.

Mo-99 breakthrough curves for such commercial manufactured lots are presented in Figure 1. The source of the Mo-99 does not affect the performance of the generator as demonstrated by this in-process quality parameter. The on-line breakthrough pattern is consistent between the lots manufactured using LEU, HEU or blended LEU/HEU Mo-99.

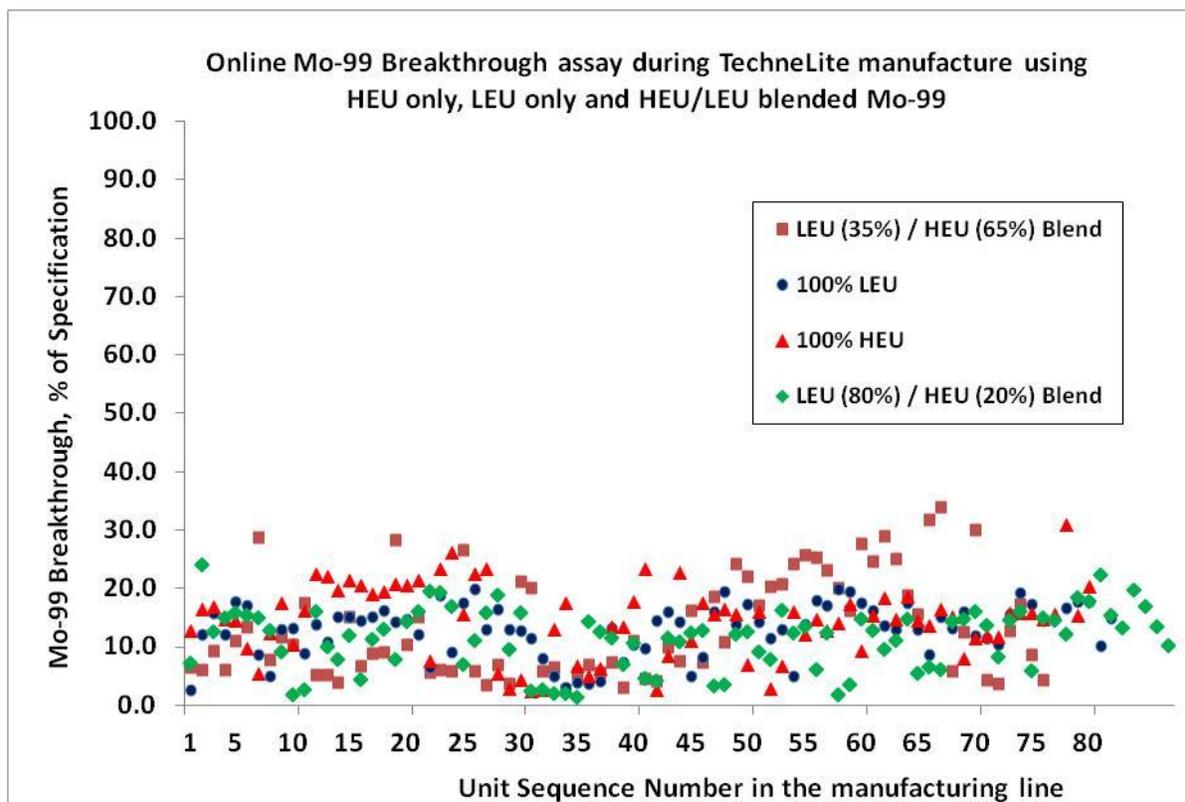


Figure 1. Mo-99 breakthrough (online assay) during commercial TechneLite[®] manufacture runs with LEU, HEU or blended LEU/HEU Mo-99.

Similarly, the generator column assay results (Figure 2) demonstrate equivalent properties and performance of the commercial generators manufactured with LEU, HEU or blended HEU/LEU Mo-99. The column assay is measured as assayed Mo-99 loaded on the column versus the required labeled activity of the unit.

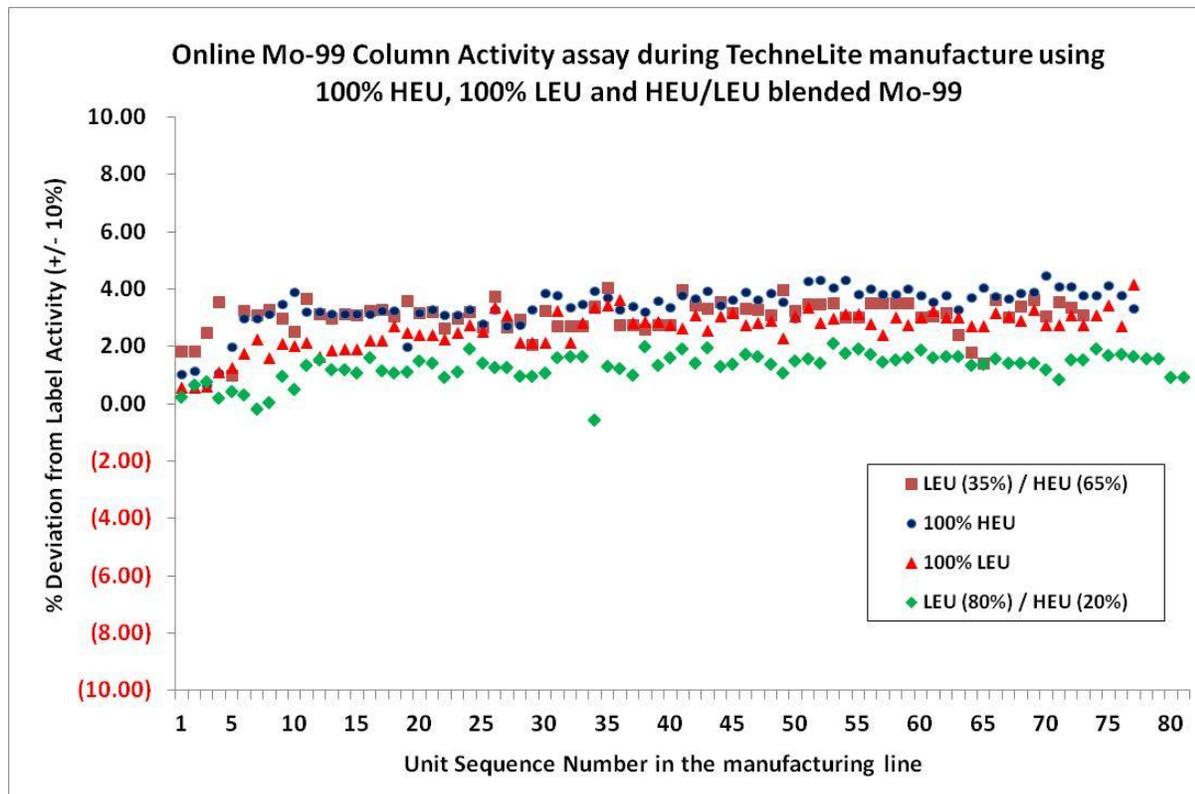


Figure 2. Mo-99 activity on the column (online assay) during commercial TechneLite[®] manufacture runs with LEU, HEU or blended LEU/HEU Mo-99.

Increased reimbursement for Tc-99m produced from non-HEU sources

In March 2012, the U.S. Government indicated that it was considering a number of options to facilitate increased use of LEU-produced Mo-99 in U.S. nuclear medicine procedures. It indicated that the higher cost of producing Mo-99 from LEU targets, as well as increased costs of Mo-99 due to the industry’s transition toward Full Cost Recovery (recommended by the High-Level Group on Medical Radioisotopes, OECD/NEA) posed a challenge to increased utilization of LEU-produced Mo-99. U.S. governmental authorities indicated that consideration was underway regarding increased reimbursement by the U.S. Medicare system of medical procedures using non-HEU produced medical radioisotopes.

As a result, the Center for Medicare and Medicaid Services (CMS, Department of Health and Human Services) proposed a \$10 “add-on” payment for non-HEU produced doses when it published its proposed rule in July 2012 for the Hospital Outpatient Prospective Payment System (HOPPS). The final rule was published in November 2012 and went into effect on January 1, 2013.

Lantheus Medical Imaging carried out an active dialogue with the U.S. Government on its own and as part of industry trade association efforts as the “add-on” payment was under consideration by CMS. Lantheus also submitted formal comments on the proposed rule to CMS

in August 2012 during the official public comment period. Lantheus expressed support for the CMS initiative in its comments to CMS and in public statements after the publication of the final rule.

During this time, Lantheus began to consider the requirements for manufacturing a TechneLite[®] generator that would meet the requirements of the CMS HOPPS rule for minimum 95% non-HEU content.

TechneLite[®] LEU Product Addition

Lantheus Medical Imaging established a Cross Functional Project Team to incorporate an LEU TechneLite[®] generator into its current manufacturing process and schedule. In order to position for LEU TechneLite[®] generator addition to the product line in January 2013, the entire Lantheus molybdenum supply chain, from the reactors (Mo-99 suppliers) through our manufacturing process, and into our distribution logistics for the delivery of the LEU TechneLite[®] generator to Customers was analyzed.

Tasks to be completed and potential barriers to the operations were identified and evaluated to successfully be able to deliver LEU TechneLite[®] generators. After careful analysis, it was determined that manufacturing an LEU TechneLite[®] generator on Monday, would be the appropriate day and timing for the initial introduction to the market. To facilitate this, changes were required to the current LEU and HEU Mo-99 purchasing schedules and arrival times, as well as changes to processes throughout the organization.

In parallel, Lantheus' Marketing Team conducted Market Research to gain insight on the knowledge and understanding of the add-on reimbursement payment for non-HEU produced Tc-99m doses at Radiopharmacies and Hospitals, and how they would implement this into their daily operations. This information was utilized to assist in the development of Marketing communications and information pieces, designed to increase customer awareness and provide support on the program to Nuclear Medicine professionals. These communications and information pieces have been made available at Industry Trade Shows, through Direct mailing and on Lantheus' TechneLite[®].com website. Many Nuclear medicine professionals have found the "HEU vs. LEU TechneLite[®]: Fact vs. Fiction" section particularly useful.

TechneLite[®] LEU Manufacturing

Lantheus began manufacturing the LEU TechneLite[®] generators with at least 95% LEU content on January 7, 2013. This is compliant with the CMS \$10 add-on payment for non-HEU generators.

Lantheus currently manufactures LEU TechneLite[®] generators in a dedicated LEU production run weekly on Mondays. On other days of the week, TechneLite[®] generator production utilizes either blended LEU/HEU Mo-99 or all-HEU Mo-99.

A validated cleaning process is completed after the prior TechneLite[®] generator production run on Saturday/Sunday. This cleaning process ensures that any carryover HEU Mo-99 is significantly below 5% quantity established by CMS for the non-HEU compliant generator.

In order to distinguish TechneLite[®] LEU generators as eligible for the CMS add-on payment, Lantheus applies a circular green sticker to the top of the TechneLite[®] generator can (Figure 3). The generator can top with the green sticker is manually installed on the generator during the final assembly operation just prior to product packaging.

This circular green sticker on the generator can cover is the only difference between the LEU TechneLite[®] generator and a blended or all-HEU TechneLite[®] generator (the product insert is identical for all these generators).

In accordance with GMP requirements, manufacturing batch records indicate by a different code that LEU-produced Mo-99 was used in the LEU TechneLite[®] generators.

The Lantheus LEU TechneLite[®] generator has a specific catalog/item number in the Lantheus product catalog. An LEU TechneLite[®] Monday generator is listed as 18000-ML while the HEU Monday generator is listed as item 18000-M. This identifying item number is also indicated on the packing and shipping documents and the Invoice. In addition, the lot number for the LEU generators also has a unique identifier. An “A” is incorporated into the generator lot number. For example, HEU generator: M123456D, Non-HEU generator: M123456A.



Figure 3. The LEU Technelite Tc-99m generator is indicated by the green dot on the top cover.

Lantheus has performed 10 manufacturing runs of LEU TechneLite[®] generators, labeled with the green sticker, as of March 22, 2013.

Mo-99 breakthrough curves for recent commercial LEU manufactured lots are presented in Figure 4. This in-process quality parameter is consistent between the three manufactured lots and further demonstrates the use of LEU Mo-99 is a viable source of Mo-99 that produces consistent quality Tc-99m generators.

Similarly, the generator column assay results (Figure 5) demonstrate equivalent properties and performance of the commercial LEU generators between the manufactured lots.

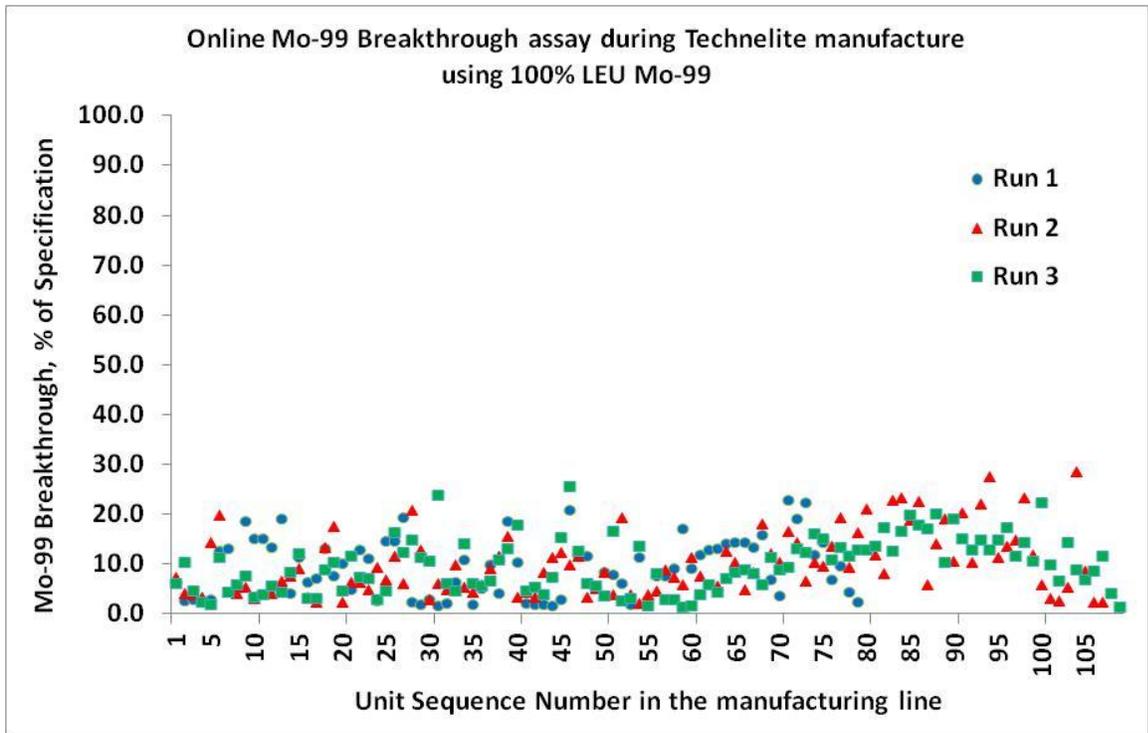


Figure 4. Mo-99 breakthrough (online assay) during commercial LEU TechneLite[®] manufacture runs (100% assay)

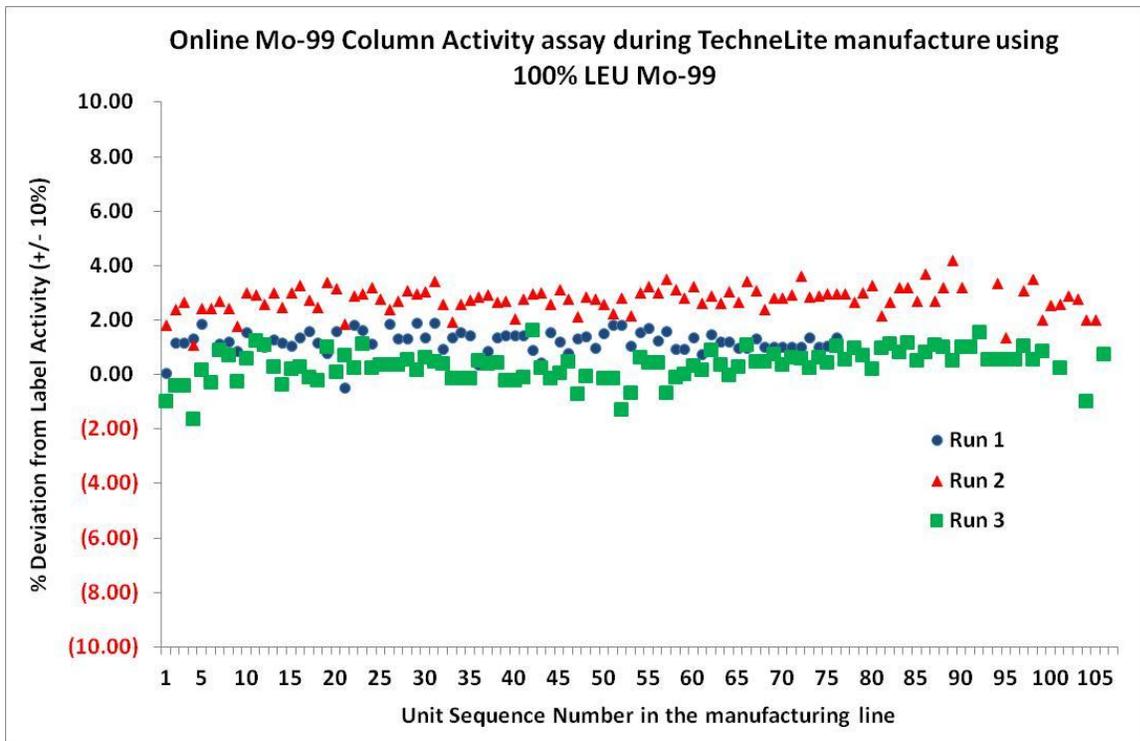


Figure 5. Mo-99 activity loaded on the column (online assay) for commercial LEU TechneLite[®] manufacture runs (100% assay)

CONCLUSIONS

As previously reported [3 and 4], the quality and properties of TechneLite[®] generators using LEU-produced Mo-99 (during both qualification and commercial production including blended LEU-HEU production since May 2011) have been proven to be equivalent to those manufactured using HEU produced Mo-99. The data presented in this paper on the manufacture of LEU TechneLite[®] generators meeting the CMS 95% LEU content criteria provides further evidence that the quality and properties of such LEU generators are equivalent to all prior manufactured TechneLite[®] generators using HEU, blended, or LEU-only Mo-99. The Tc-99m produced from such 95% content TechneLite[®] generators meets all requirements of the USP.

Lantheus has consistently taken a leadership role in the commercial introduction and use of LEU Mo-99 in its TechneLite[®] generator supply chain. The dedicated production of LEU TechneLite[®]Tc-99m generators since early January 2013 hastens our transition toward an eventual all-LEU Mo-99 supply chain by the end of 2016.

Lantheus believes that this development not only makes a positive contribution toward enhanced global nuclear security but also creates a foundation for a more secure and reliable future supply of Mo-99, which benefits our customers and patients.

REFERENCES

1. Lantheus Medical Imaging press Release, 23 June 2009, “Lantheus Medical Imaging, Inc. to receive LEU-Derived Mo-99 from Australian Nuclear Science and Technology Organisation (ANSTO) and becomes first to supply U.S. Market” (2009)
2. Lantheus Medical Imaging Press Release, 6 December 2010, “Lantheus Medical Imaging announces first commercial production of TechneLite[®] generators from low-enriched uranium-produced molybdenum-99” (2010)
3. “Qualification of LEU Produced Mo-99 TechneLite[®] Generators for National Health Regulatory Approval,” 1st Annual Mo-99 Topical Meeting, December 4-7, 2011, Santa Fe, New Mexico
4. “Experience from Routine Commercial Use of LEU-Produced Mo-99 in TechneLite[®] Generators”, Transactions of the American Nuclear Society, vol 107, San Diego, California, November 11-15, 2012
5. Lantheus Medical Imaging Press Release, 9 January 2013, “Lantheus Medical Imaging Introduces Low-Enriched Uranium (LEU) Technelite[®] Generator (2013)