

**Mo-99 2014 TOPICAL MEETING ON
MOLYBDENUM-99 TECHNOLOGICAL DEVELOPMENT**

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TechneLite[®] Generators Manufactured with LEU-based Mo-99

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ABSTRACT

Lantheus Medical Imaging, Inc. added TechneLite[®] (Tc-99m generator) manufactured using molybdenum-99 (Mo-99) produced from Low-Enriched Uranium (LEU) to its product portfolio in January 2013 as evidenced by the shipment of its first “LEU TechneLite[®] generator”. This “LEU generator” has been demonstrated to be equivalent in performance and use to the TechneLite[®] manufactured with Highly Enriched Uranium (HEU) sourced Mo-99. Tc-99m from the “LEU TechneLite[®]” meets all requirements of the USP. TechneLite[®] generator manufactured using a blend of HEU and LEU sourced Mo-99 was approved by the FDA in 2010, and such generators have been commercially available in the US since 2011.

Lantheus announced in 2012 additional access to LEU sourced Mo-99 from NTP Radioisotopes (South Africa). Currently, Lantheus receives Mo-99 from four major processors and seven associated reactors, and an increasing supply of Mo-99 from LEU targets from NTP as well as ANSTO (Australia) will be received over the next five years. Lantheus continues to receive HEU sourced Mo-99 from Nordion which supports its diverse Mo-99 supply chain.

The “LEU TechneLite[®]” is manufactured in a dedicated manufacturing run and the generator has a unique product item number. NDC numbers have been established for the LEU generators and these will be reflected in the revised package insert. This helps the radiopharmacies and hospitals to file for the Centers for Medicare and Medicaid Services (CMS) incremental reimbursement provided for each Tc-99m diagnostic dose produced from non-HEU sourced Mo-99.

The progress Lantheus has made since the 2013 “LEU TechneLite[®]” product addition, the transition toward an eventual all-LEU Mo-99 supply chain and a radiopharmacy’s experience with implementation of the “LEU TechneLite[®] Generator” into its operations and product supply to the Company’s customers will be discussed.

INTRODUCTION

Lantheus Medical Imaging (LMI) has been providing TechneLite[®] LEU generators produced using molybdenum-99 (Mo-99) sourced from at least 95 percent Low-Enriched Uranium (LEU) targets since January 7, 2013 [1]. Routine commercial production and delivery of TechneLite[®] Tc-99m generators manufactured using Mo-99 from LEU targets was begun in May 2011, but was at that time blended with Mo-99 produced from Highly Enriched Uranium (HEU targets). The “all-LEU” and standard HEU-produced TechneLite[®] generators are equivalent in performance and use as recognized by U.S. Food and Drug Administration (FDA) approval of LEU-produced Mo-99 generators. The 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 January 1, 2013 Hospital Outpatient Prospective Payment System (HOPPS).

Both HEU and LEU TechneLite[®] generators are produced at LMI’s state-of the art manufacturing facility in Massachusetts and the LMI Mo-99 specification for a qualified supplier is based on the European Pharmacopeia Mo-99 monograph. The qualification of LEU Mo-99 for use in the TechneLite[®] generator 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) [2-4]. Lantheus has an internal protocol which governs the process for the qualification of new Mo-99 suppliers and/or sources and is based on FDA recommendations/guidance. The line is semi-automated and runs through 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). Subsequent quality control (QC) and release testing include testing of functional operation, Tc-99m eluate pH, chemical purity, radiochemical and radionuclidic purity, radionuclidic ID, Mo-99 breakthrough, sterility, and endotoxin levels at Date of Manufacture (DOM) that ensure the product quality is consistent and within specifications.

The differentiating feature between the LEU TechneLite[®] and the standard TechneLite[®] generator (using HEU sourced Mo-99) is a visual identifier that is a large, round green “dot” sticker on the top of the LEU TechneLite[®] generator can. The LEU TechneLite[®] generator has the same label and package insert as the standard TechneLite[®] generator.

RESULTS AND DISCUSSION

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

Lantheus qualified LEU sourced Mo-99 for use in the TechneLite[®] generator 2010-2011 in close collaboration with NTP and ANSTO. Mo-99 was provided free of charge by NTP and ANSTO for all the non-commercial validation and qualification runs which was a considerable expense for both parties as they produced hundreds of curies of Mo-99 for use in the qualifications. These runs consisted of Mo-99 produced only from LEU targets, and was not mixed with HEU Mo-99. All qualification runs were conducted on the commercial LMI

manufacturing line. The qualification of the two Mo-99 suppliers took about a year and a half from the first evaluation run to the FDA approval and the receipt of the No Objection Letter from Health Canada.

Since then TechneLite[®] generators have been 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. Tests are done between all runs to ensure there is no carryover of Mo-99 and that the level is significantly below 5% quantity established by CMS for the non-HEU compliant generator and that the system and lines are clean. The purchased Mo-99 originating from HEU and LEU Mo-99 sources in 2011 was in an average ratio of 92%/8% and 88%/12% in 2012. In 2013, LEU Mo-99 accounted for <30% of LMI's Mo-99 purchases.

Lantheus began manufacturing LEU TechneLite[®] generators which meet the requirements of the Center for Medicare and Medicaid Services (CMS, Department of Health and Human Services) \$10 “add-on” payment rule for non-HEU produced doses for the Hospital Outpatient Prospective Payment System (HOPPS) for minimum 95% non-HEU Mo-99 content on January 7, 2013.

Currently, as the introduction to the market, the LEU TechneLite[®] generator is manufactured on a dedicated Monday production run. This was accomplished by changing the current LEU and HEU Mo-99 purchasing schedules and material arrival times on site, as well as changing several processes throughout the organization. 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.

The TechneLite[®] LEU generators are distinguished from the standard generator by a circular green sticker on top of the TechneLite[®] generator can. This indicates the generator is eligible for the CMS add-on payment and 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). The LEU TechneLite[®] generator also has a specific catalog/item number in the Lantheus product catalog.

TechneLite[®] LEU Manufacturing

Lantheus has performed 55 manufacturing runs of LEU TechneLite[®] generators, labeled with the green sticker, as of June 23, 2014.

Every TechneLite[®] generator that is manufactured on the LMI line is monitored for the level of Mo-99 breakthrough on-line shortly after loading of Mo-99 on to the alumina column. The on-line Mo-99 breakthrough pattern is consistent between the lots manufactured using 100% HEU sourced Mo-99, 100% LEU and blended HEU/LEU (Figure 1). The Mo-99 breakthrough test is very sensitive and some variability into the results is introduced due to the nature of radioactivity assay, time of assay and the amount of Mo-99 activity loaded on the generator, but

the results demonstrate LEU Mo-99 as a viable source of Mo-99 that produces consistent quality Tc-99m generators. [5]

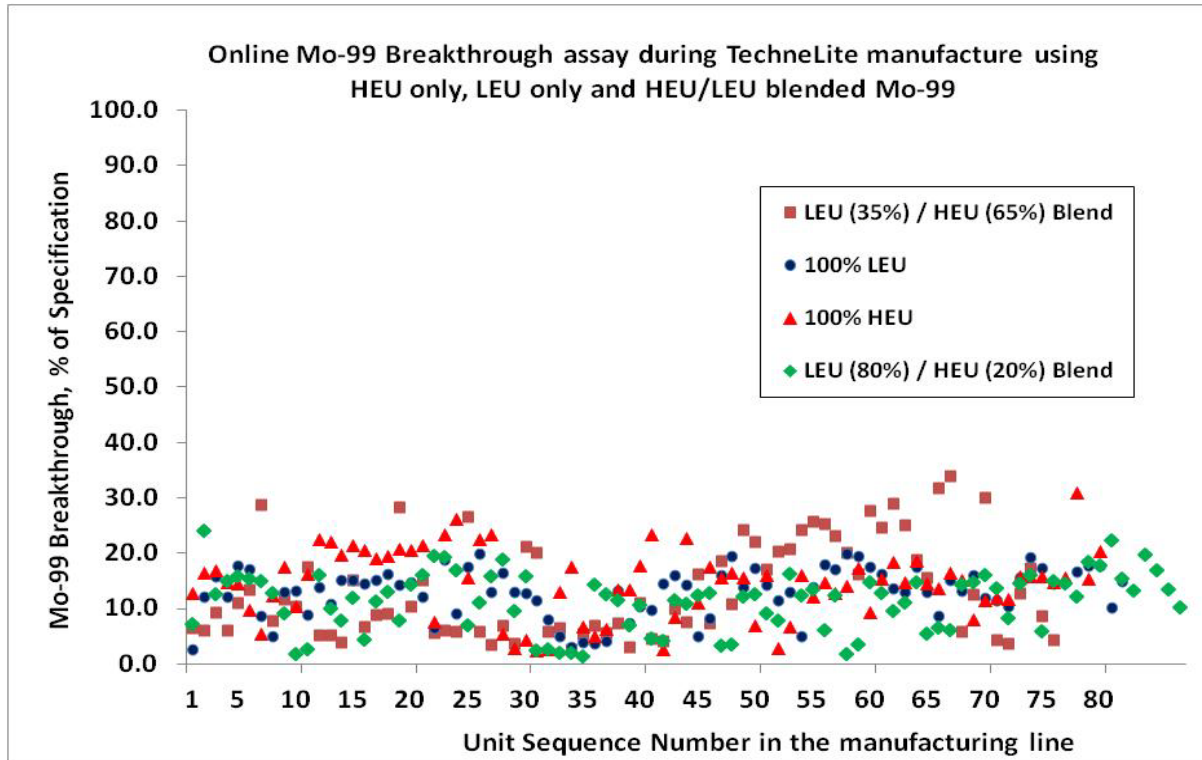


Figure 1. Mo-99 breakthrough (online assay) during commercial TechneLite[®] manufacture runs with LEU, HEU or blended LEU/HEU Mo-99.

The increase in LEU TechneLite[®] generators shipped to customers over the past two years has been gradual, but indicating a clear increase in orders. The demand for LEU generators has been somewhat impacted by the variable reliability of the LEU sourced Mo-99 supply, but as implied by the shown trends in Figures 2 and 3, it can be expected this increase will continue as the supply becomes more established.

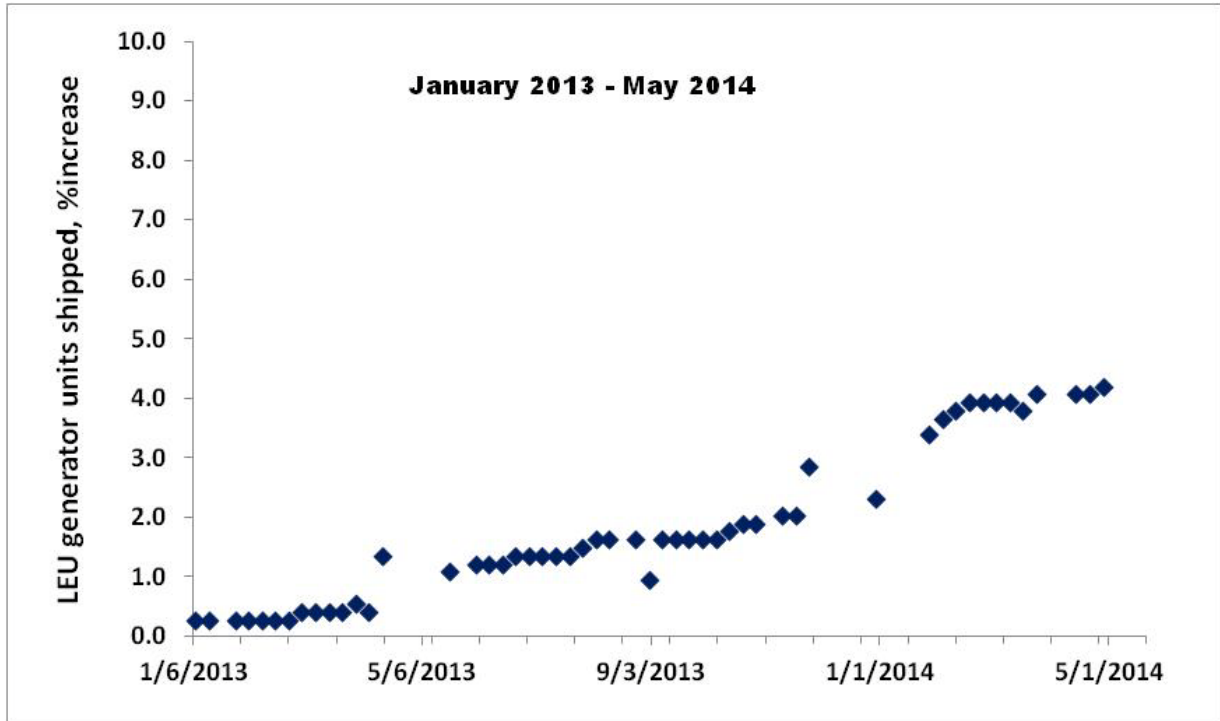


Figure 2. Increase in LEU Mo-99 TechneLite[®] generators shipped over the review period

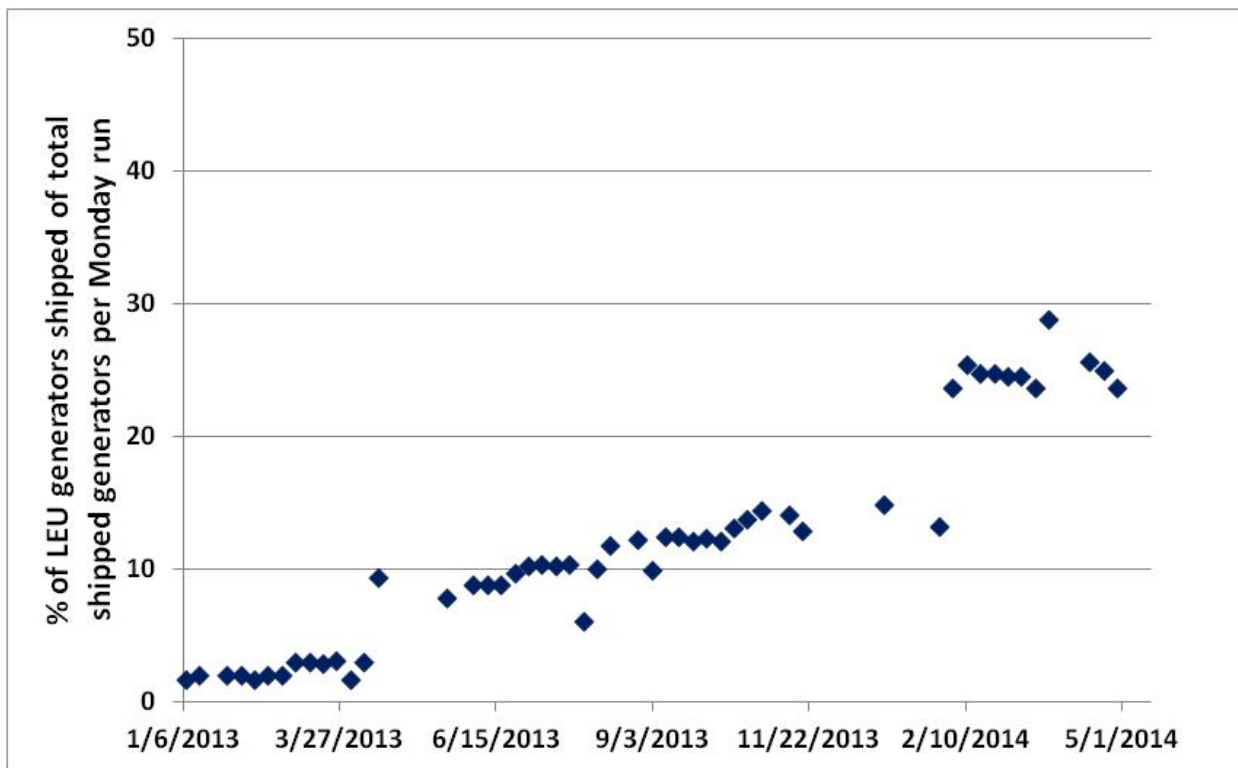


Figure 3. Increase (%) in shipped LEU TechneLite[®] generators per manufacture run

TechneLite® LEU Experience at a Radiopharmacy

Lantheus (which operates radiopharmacies in Puerto Rico) together with customers purchasing LEU generators have gained significant insight and experience regarding utilization of LEU generators in the radiopharmacy setting. Both independent pharmacies and the Center for Medicare and Medicaid Services (CMS) have reported that end-users are applying for and are receiving the \$10 add-on reimbursement payment for non-HEU produced Tc-99m doses. In addition, pharmacies using LEU TechneLite® generators have indicated that they have made changes in information management systems that allow them to segregate and track doses produced from LEU-produced TechneLite® generators.

The experience of the end-user of using the LEU TechneLite® generators was observed at two different radiopharmacies. The Tc-99m elution efficiency (%) is the indicator used to evaluate and monitor consistent performance of a generator throughout its expiry. Although there is no specification for generator efficiency (or Tc-99m yield), the value based on historical performance of the TechneLite® generator manufactured with HEU Mo-99 has been >85% [6]. All units monitored at the two radiopharmacies demonstrated performance that was consistent with this expectation.

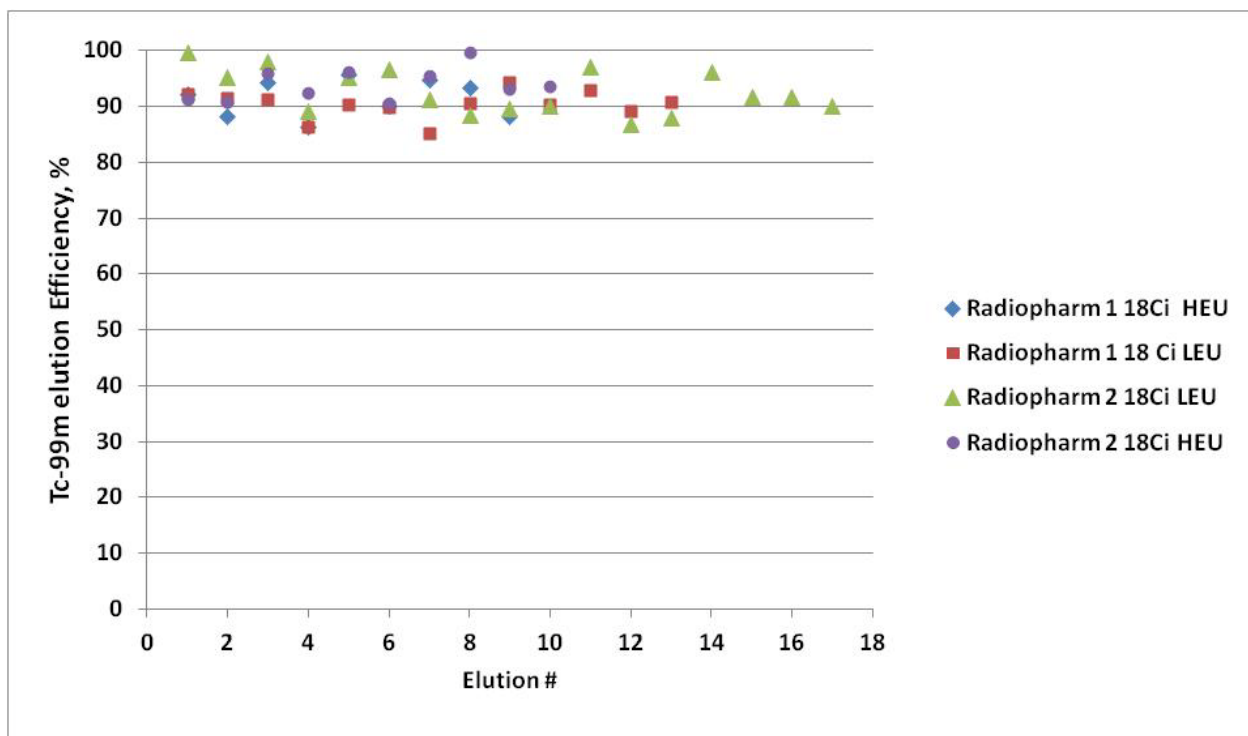


Figure 4. Tc-99m elution efficiency of 18Ci TechneLite® generator units manufactured using 100% HEU Mo-99 and 100% LEU Mo-99 as eluted at two different radiopharmacies

CONCLUSIONS

The data presented in this paper on the manufacture of LEU TechneLite[®] generators meeting the CMS 95% LEU content criteria demonstrates that the generators manufactured using LEU or blended HEU/LEU sourced Mo-99 have comparable properties to TechneLite[®] generators manufactured using ‘standard’ HEU Mo-99. The Tc-99m produced from these TechneLite[®] generators meets all requirements of the USP. Further, radiopharmacies using LEU TechneLite[®] generators report that they have been able to successfully integrate such generators in their operations without added complexity and that customers are receiving the additional \$10 CMS add-on payment for non-HEU doses.

Lantheus and its LEU supply partners are working closely together to improve the consistency and reliability of the LEU supply chain. Based on customer demand and other factors, Lantheus will consider manufacturing LEU generators on additional day(s).

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 supports our goal of transitioning toward an eventual all-LEU Mo-99 supply chain.

REFERENCES

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