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Qualification of LEU Produced Mo-99 TechneLite® Generators for National Health Regulatory Approval

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ABSTRACT

This paper describes the qualification process for obtaining U.S. and Health Canada approval for the commercial sale of Lantheus Medical Imaging TechneLite® Tc-99m generators manufactured using Mo-99 produced from the irradiation and processing of Low-Enriched Uranium (LEU) targets by NTP Radioisotopes Pty Ltd. (South Africa) and ANSTO Health (Australia). The paper will briefly describe the coordinated technical, manufacturing, and regulatory steps and schedule that were carried out by the various organizations in order to obtain regulatory approval for commercial use of LEU produced Mo-99. This includes changes to the respective Drug Master Files (DMF); performance of non-commercial and commercial qualification runs; testing and quality control activities and results; informal communications with and other required formal filings to regulatory agencies. The paper provides general guidance for future qualification efforts and concludes that the quality and properties of TechneLite® generators using LEU-produced Mo-99 are equivalent to those produced using HEU produced Mo-99.

1. Introduction

Typically, discussions concerning technical and financial aspects of conversion of Mo-99/Tc-99m production from Highly Enriched Uranium (HEU) to Low Enriched Uranium (LEU) have focused on LEU targets, changes to the isotope separation process, and waste management. These activities require various nuclear regulatory approvals in countries carrying out Mo-99 irradiation and production. As the Tc-99m generator is a regulated radiopharmaceutical, Tc-99m generator manufacturers lead a challenging regulatory process in cooperation with the Mo-99 producers in order to bring to patients Tc-99m from generators using LEU-produced Mo-99.

Lantheus Medical Imaging, Inc. (Lantheus), based in North Billerica, Massachusetts, is a worldwide leader in diagnostic medicine, that is dedicated to creating and providing pioneering medical imaging solutions to improve the treatment of human disease. Lantheus has been a leader in the nuclear medicine industry for more than 50 years, beginning as New England Nuclear. The TechneLite®, Technetium Tc99m Generator is produced at a state-of the art, world-class manufacturing facility in Massachusetts and distributed to North America, Asia, and Latin America. Lantheus also operates radiopharmacies, which prepare unit doses in Canada, Puerto Rico, and Australia.

NTP Radioisotopes (Pty) Ltd. (NTP) is a limited liability company and a wholly owned subsidiary of the South African Nuclear Energy Corporation (Necsa). It operates the SAFARI-1 research reactor and its primary focus is the production and distribution of various radiochemicals to both the medical and industrial sectors. NTP also produces various radiopharmaceuticals such as its locally developed NovaTec-P Tc-99m generator, F-18 based PET products and I-131 capsules and solutions.

The Australian Nuclear Science and Technology Organisation (ANSTO) is the only nuclear research facility in Australia and the center of its nuclear expertise, specializing in the applications of nuclear science. ANSTO is owned by the Australian Government and provides a broad range of radiopharmaceuticals and radiochemicals for the Australian, New Zealand and other Asian markets. ANSTO produces radioisotopes in the OPAL multi-purpose research reactor commissioned in 2007 at Lucas Heights, about 40 minutes south of Sydney.

Lantheus and its predecessors historically acquired bulk Mo-99 from Nordion Inc. and Atomic Energy of Canada Limited (AECL) NRU reactor for manufacture of TechneLite® generators. In order to establish a globally diversified Mo-99 supply chain, Lantheus qualified HEU-produced Mo-99 from NTP and its subcontractor the National Institute for Radioelements (IRE, Belgium) and began regular Mo-99 purchases in early 2009. Lantheus announced in June 2009 that it had reached agreement with ANSTO to receive Mo-99 produced from LEU targets [1].

In October 2009 NTP received South African nuclear regulatory approval and commenced the hot test phase of a project to convert Mo-99 production to the use of LEU targets [2]. Lantheus and NTP consequently began discussions to qualify LEU-produced Mo-99 for use in Lantheus TechneLite® generators with the goal of obtaining U.S. Food and Drug Administration (FDA) and Health Canada (HC) approval for their commercial sale in the U.S. and Canada.

It should be noted that these activities occurred during significant international shortages of Mo-99 from May 2009 to mid-August 2010. The NRU research reactor at Chalk River, Canada was shut-down for repairs as a result of a heavy water leak. An outage due to repairs of the HFR reactor in Petten, Netherlands also occurred from February-September 2010.

2. Regulatory and Qualification Process

a. Regulatory Requirements

The FDA and HC (HC) have similar requirements for the approval for commercial use of LEU-produced Mo-99. The Mo-99 producer provides a Drug Master File (DMF) which includes detailed information with regard to the irradiation, processing, and purification including shipping of Mo-99 to the generator manufacturer. The DMF is not reviewed by the FDA until a submission (by the generator manufacturer) is made referencing the DMF. The Mo-99 producer sends a letter to the FDA giving permission for the generator manufacturer to be given access to the applicable proprietary portion(s) of the DMF. During the period of FDA review of the generator manufacturer submission, questions concerning the DMF may be raised by the FDA which can slow down the approval process.

The generator manufacturer is required to provide information to both the FDA and HC to demonstrate that Tc-99m produced from the LEU Mo-99 generator meets the regulated specifications (same as for a generator manufactured from HEU-produced Mo-99) and that it does not contain radionuclidic impurities greater than that specified in the US Pharmacopeia monograph for Tc-99m (Note: HC indicated particular interest regarding compliance with gross alpha due to potential contribution of Pu-239). The generator manufacturer also must demonstrate chemical equivalence in side-by-side comparison of the specifications and results from using the Tc-99m to radiolabel kits containing anionic, cationic and neutral ligands. FDA and HC have required the generator manufacturer to conduct three independent qualification generator manufacturing runs to produce the required data.

The required information is formally submitted to the FDA in the form of a Prior Approval Supplement in accordance with 21 CFR § 314.70 and as a Notifiable Change to HC.

In order to facilitate the regulatory process for LEU-produced Mo-99, Lantheus found it helpful to maintain regular contact with FDA and HC prior to and during the regulatory review process.

b. Lantheus Qualification Protocol Testing Performed

The Lantheus 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. This protocol is designed to ensure the generation of data to meet evolving requirements for FDA and HC regulatory submissions. The Lantheus protocol includes the following routine testing:

- In-process formulation and filling – pH, Mo-99 batch activity concentration (HPGe detector or ionization chamber), Mo-99 breakthrough (Single Channel Analyzer) and generator column assay (ion chamber)
- QC release testing (functional, eluate description, pH, chemical purity, radiochemical and radionuclidic purity, radionucludic ID, Mo-99 breakthrough, sterility, endotoxin) at Date of Manufacture (DOM) Stability testing includes; all QC release testing repeated at Date of Expiry (14 days post DOM), plus beta testing at DOM and DOE
- Customer use elution simulation testing (performed at three timepoints)
- Kit compatibility testing (anionic, cationic and neutral kits at T0 and expiry)
- Microbiological testing (Bacteriostasis and Fungistasis)

In the case of both NTP and ANSTO LEU-produced Mo-99, LMI also carried out certain "non-routine" testing (for information purposes only as there is no regulatory specification) in the form of ICP spectrometry for the presence of tungsten (elemental analysis) in a sample from the final Mo-99 bulk formulation solution and in generator eluate(s).

3. NTP LEU Qualification

Lantheus and NTP began discussions regarding LEU qualification in late 2009. South Africa prepared a revised DMF (as compared to the DMF on file for HEU-produced Mo-99) and submitted it to the FDA. Evaluation and qualification had to be carefully scheduled between normal HEU-based production during the period of the Mo-99 shortage as such runs had to consist of Mo-99 produced only from LEU targets and could not be mixed with other Mo-99 sources. The qualification runs were scheduled for days when there was no Lantheus commercial generator production using HEU-produced Mo-99. The steps and timeline involved in the qualification and approval process for NTP LEU-produced Mo-99 is described in Figure 1.

Figure 1 – NTP Qualification Timeline

Action	Quantity	Date	Remarks
Evaluation run	32 (1-20Ci)	February 1, 2010	Full scale, but reduced testing DOM only (with customer use and sestamibi); no sterility or endotoxin
Qualification run 1	38 (1-20Ci)	July 22, 2010	Full scale, non-commercial, full testing
Prior Approval Supplement		September 8, 2010	Submitted to FDA
Supplement Approval		September 28, 2010	FDA approval
Qualification run 2	35 (1-20Ci)	September 30, 2010	Full scale, non-commercial*, full-testing
Notifiable Change (HC)		November 25, 2010	Results of 3 qualification lots
Qualification run 3	291 (1-20Ci)	December 6,, 2010	Full scale, commercialized within US; robust testing
Notifiable Change (HC)		March 15, 2011	Health Canada No Objection letter
Routine shipments		Late May 2011	Commercial

*FDA approval had been received and this run could have been commercialized

4. ANSTO LEU Qualification

Lantheus and ANSTO initiated discussions starting in 2007 concerning potential supply of LEU-produced Mo-99 from ANSTO's new Mo-99 processing facility constructed by INVAP SA in association with the OPAL research reactor. A non-commercial evaluation run (only 1 and 2 Ci generators manufactured, batch concentration was at $1/10^{th}$ commercial levels, no sterility, endotoxin or QC expiry timepoint testing) was executed on January 16, 2009. Following discussion with the FDA, a Changes Being Effected – Expedited Review Requested Supplement was submitted to the FDA on June 18, 2009. Due to the prevailing Mo-99 shortage situation due to the NRU outage, FDA granted concurrent approval to allow the use of ANSTO LEU-produced Mo-99 in commercial Lantheus TechneLite® generators on the basis of data submitted from the single evaluation run [1]. However, FDA still required data and an additional submission for three full-scale, independent qualification runs.

After this approval and through 2009, ANSTO performed one-two Mo-99 production runs per week [3, 4]. This product was required for the Australian domestic market. Regular discussions between Lantheus and ANSTO and with FDA resulted in a decision to carry out additional evaluation runs. These were to include the evaluation and qualification of an additional target plate supplier (CERCA, France) which had not been included in the original DMF.

An evaluation run was originally scheduled to take place in late 2009 but was not able to be performed until April 6, 2010 after a Lantheus visit to ANSTO in March 2010 for technical discussions. Figure 2 provides information regarding the other evaluation and qualification runs and the dates of FDA and HC submissions and approvals.

Figure 2 – ANSTO Health Qualification Timeline

Action	Targets/Quantity	Date	Remarks
Evaluation run 1	CERCA; 13 (1-2Ci)	April 6, 2010	Non-commercial, 1/10th conc. DOM only (customer use and sestamibi); no sterility, endotoxin
Evaluation run 2	CNEA; none	January 5, 2011	1/10th conc. due to limited activity
Qualification run 1	CNEA; 38 (1-20Ci)	January 20, 2011	Non-commercial, full testing
Qualification run 2	CNEA/CERCA; 35 (1-20Ci)	February 3, 2011	Non-commercial, full testing
Qualification run 3	CERCA; 37(1-20Ci)	March 30, 2011	Non-commercial, full testing
Prior Approval Supplement		March 11, 2011	Submitted to FDA
Notifiable Change		March 28, 2011	Submitted to Health Canada
Supplement Approval		May 4, 2011	FDA Approval Letter
Notifiable Change		May 30, 2011	Health Canada No Objection Letter
Routine Shipments		Late May 2011	Commercial

5. Results

The figures below present data obtained from Lantheus testing of TechneLite® generators manufactured with NTP and ANSTO LEU-produced Mo-99 during the qualification runs. The test results are compared with data from tests conducted during prior TechneLite® generator commercial production using NTP HEU-produced Mo-99 (for which Lantheus conducts column assay and Mo-99 breakthrough testing on 100% of units). Figure 3 shows data on Mo-99 breakthrough as compared to the USP monograph specification (noted as "Limit" with black horizontal line). Figure 4 presents data obtained from testing of three kits (anionic, cationic and neutral) during the qualification runs as compared with such testing of commercial production of generators using HEU-produced Mo-99. Both of these test sets meet the required specifications.

Figure 3 – Comparison of Run Average Mo-99 Breakthrough results on TechneLite® Generator runs manufactured using HEU vs. LEU Mo-99

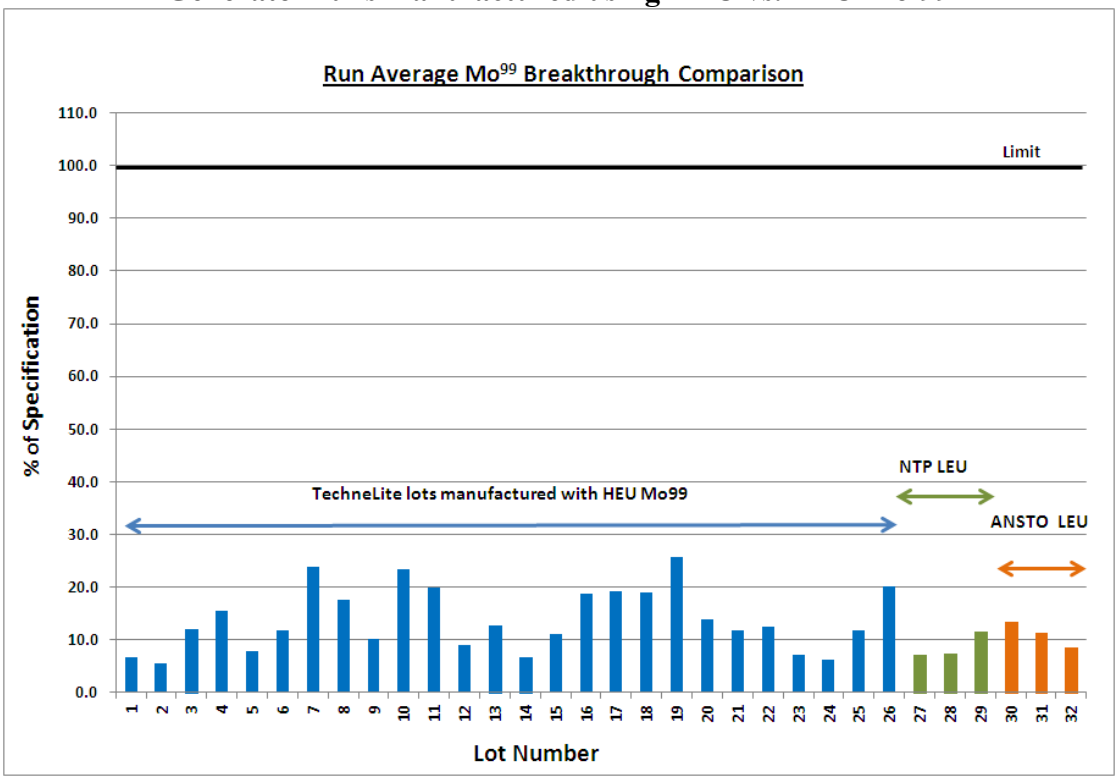
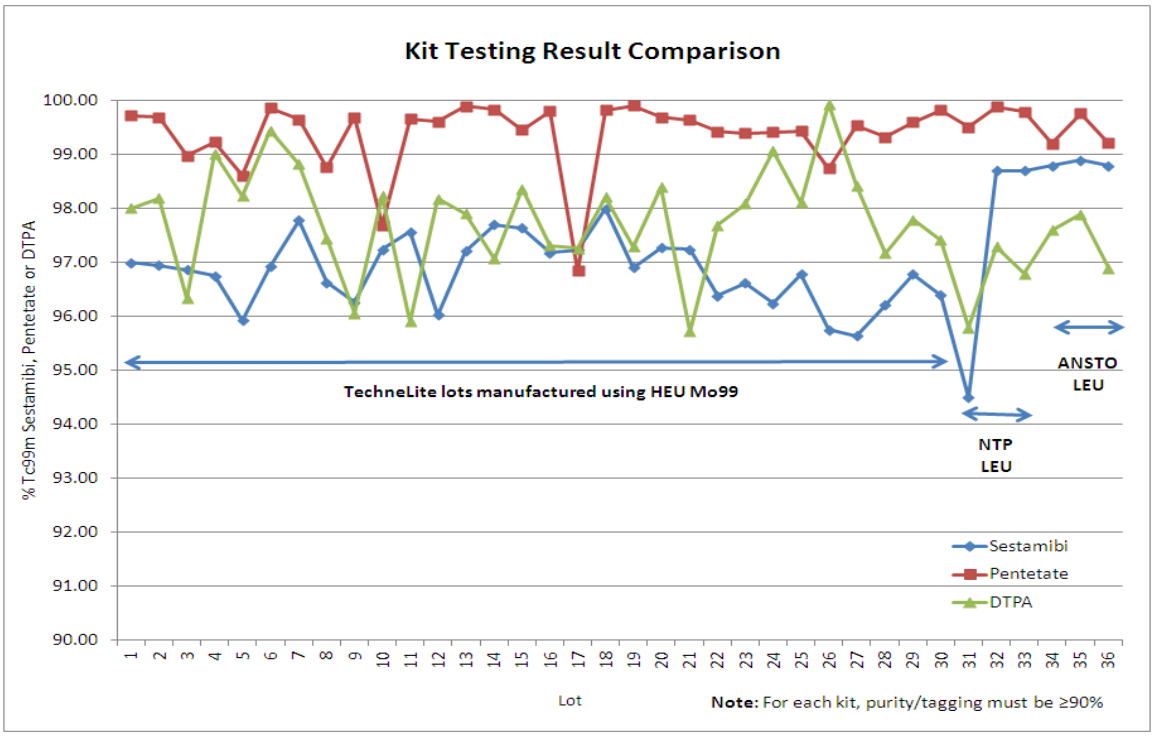


Figure 4 – Comparison of Kit Testing results on TechneLite® Generator runs manufactured using HEU vs. LEU Mo-



An issue that arose early in the qualification process with NTP and then also with ANSTO was related to the presence of W-187 (and elemental tungsten) in the Mo-99 solution. NTP reported a W-187 result above the specification limit for the Mo-99 provided for the February 1, 2010 evaluation run. ANSTO also encountered slightly elevated levels of W-187 and elemental tungsten in its production in late 2009 and early 2010. In both cases, the W-187 and elemental tungsten was traced to issues related to target manufacture and material. Changes made to that process have led to reduction of tungsten in the target plates. Lantheus testing demonstrated that the presence of tungsten (ppm levels) did not affect the process or the quality of the final product (TechneLite® generator or the Tc-99m eluate) in the February 2010 NTP qualification run or in later runs.

6. Conclusions and Summary

The most important conclusion is that the quality and properties of TechneLite® generators using LEU-produced Mo-99 are equivalent to those manufactured using HEU produced Mo-99.

The process required approximately 10-11 months from the beginning of preparatory discussions between Lantheus and NTP, or eight months from the first evaluation run to the receipt of FDA approval for NTP-produced Mo-99. In the case of ANSTO, the formal qualification process including both LEU targets required about four months for FDA and 5 months for HC. However, this had been preceded by substantial prior discussion and activity.

Several items should be taken into account in regard to using these two qualifications as a guideline for future LEU qualifications. First, it should be recognized that these timeframes included in some cases expedited review and approval by the FDA and HC due to global Mo-99

shortages as compared to the time required for review processes during normal Mo-99 supply. In addition, NTP had an established record as an international producer of Mo-99 and had prior approval for the use of HEU-produced Mo-99 in the U.S. market.

Mo-99 was provided free of charge by NTP and ANSTO for all non-commercial validation and qualification runs. NTP and ANSTO therefore bore considerable expense in producing and transporting the Mo-99 used in the qualifications, which totaled many hundreds of curies.

For Lantheus, the cost of the qualification efforts consisted of the following elements:

- Manufacturing costs for each generator run – including allocated labor and overhead divided by the number of generator runs per year
- ”Cold” parts (columns, shielding and generator casing)
- Evacuation and saline vials
- Waste disposal
- Administrative and regulatory costs – including coordination and planning with production partners, legal, and 50-70 hours of regulatory support (preparation of documents and filings, discussions with regulatory authorities, etc)

The total cost to Lantheus of the aggregate qualification process for NTP and ANSTO LEU Mo-99 was in the range from $250,000- $500,000.

It should be understood that other generator producers must undertake separate qualification of a new Mo-99 supply including LEU-produced Mo-99 in order to allow commercial use of such Mo-99 in their own generators.

7. Acknowledgements

The authors would like to recognize the excellent cooperation and collaboration between Lantheus, NTP, and ANSTO that resulted in the successful execution of the health regulatory process and approval for the commercial production of TechneLite® Tc-99m generators using LEU-produced Mo-99. The authors would also like to acknowledge and thank relevant officials of the FDA and HC for their efforts and cooperation in expediting review and approvals in this process. The authors and organizations are proud that their efforts resulted in the first commercial approval for the use of LEU-produced Mo-99 in North America, thus laying the foundation for a more secure and reliable future supply of Mo-99 benefiting customers, individual patients, and global efforts to enhance nuclear security.

8. References

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